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Review Article

Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Sentinel node mapping allows an accurate identification of nodal disease in the pelvic area in comparison to lymphadenectomy.
- Sentinel node mapping is non inferior to lymphadenectomy in terms of para-aortic detection rate.
- Sentinel node mapping does not increase nodal-specific recurrence.

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ABSTRACT

Sentinel node mapping is increasingly being utilized for endometrial cancer staging. However, only limited evidence supporting the adoption of sentinel node mapping instead of conventional lymphadenectomy is still available. Here, we aimed to review the current evidence comparing sentinel node mapping and lymphadenectomy in endometrial cancer staging. This systematic review was registered in the International Prospective Register of Systematic Reviews. Six comparative studies were included. Overall, 3536 patients were included: 1249 (35.3%) and 2287 (64.7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03; (95%CI: 1.30 to 3.18); $p = 0.002$). No difference in detection of positive nodes located in the paraaortic was observed (OR: 93 (95% CI: 0.39 to 2.18); $p = 0.86$). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95%CI: 0.58 to 1.38); $p = 0.63$). Similarly, nodal recurrences were statistically similar between groups (1.2% vs. 1.7%; OR: 1.51 (95%CI: 0.70 to 3.29); $p = 0.29$). In conclusion, our meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to asses long term effectiveness of sentinel node mapping.

Contents

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1. Introduction

Endometrial cancer represents the most commonly diagnosed gynecological malignancies in developed countries, accounting for approximately 63,000 newly diagnosed cases in 2018, in the United States (U.S.) [1]. Data from the U.S. cancer statistics, suggested an increase in endometrial cancer incidence, with an increase of >23,000 newly diagnosed cases/year in the last decade [1,2].

Surgery is the mainstay of treatment for endometrial cancer [3]. Hysterectomy with or without bilateral salpingo-oophorectomy allows the removal of the tumor and its classification on the basis of histology, grade, and depth of myometrial invasion. The role of retroperitoneal staging is still controversial [4]. Although nodal status has a certain prognostic role, two randomized trails comparing hysterectomy plus node dissection vs. hysterectomy alone failed to suggest a beneficial role of nodal dissection [5,6]. Theoretically, lymph node dissection allows to identify patients with disease harboring in the lymph nodes, thus allows tailoring further adjuvant treatments after surgery.

Recently, sentinel node mapping replace full lymphadenectomy in low risk and also high-risk endometrial cancer patients. Growing evidence suggested the non-inferiority of sentinel node mapping in endometrial cancer [7]. In 2018, the National Comprehensive Cancer Network (NCCN) guidelines approved the execution of sentinel node mapping for endometrial cancer staging procedures for low- and high-risk endometrial cancer [8].

The main advantage of adopting sentinel nodes regards pathological ultrastaging with the detection of low volume disease not detectable by conventional histological examination executed in case of full lymphadenectomy [9,10]. Additionally, avoiding full lymphadenectomy resulted in a decrease of surgery-related morbidity and long-term complications of lymphadenectomy (i.e., lymphoedema, lymphorrhea, lymphoceles) [4].

Although accumulating data underlined the safety and effectiveness of sentinel node mapping, only few comparative studies (comparing sentinel node mapping vs. lymphadenectomy) are still available. Here, we aimed to review current evidence on sentinel node mapping in comparison to conventional lymphadenectomy. As secondary endpoint measure we sought to assess non-inferiority of sentinel node mapping in comparison to conventional lymphadenectomy in terms of positive node(s) detection rate and survival outcomes.

2. Methods

2.1. Study eligibility

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID: #119651). A protocol was defined prior to the search include the population criteria, description of interventions, comparisons, and the outcomes of interest. Our systematic review was following the suggestions from the Preferred Reporting Items for Systematic Reviews and Meta-examinations (PRISMA) statement [9]. Per protocol inclusion and exclusion criteria was the following. Inclusion criteria: comparative studies, English language, and >10 cases. The exclusion criteria were: case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies.

2.2. Literature search

The search was performed comprehensively, using several databases from each database's earliest inception to December 2018; the following controlled keywords were used: “Sentinel node mapping”, “Uterine cancer”, “Endometrial cancer” and “Lymphadenectomy” to search, PubMed (MEDLINE), Scopus and Web of Science databases as well as ClinicalTrials.com (www.clinicaltrials.com). The search strategy was designed the study's principle investigator and conducted by all the other authors.

2.3. Study selection

Selection of studies was conducted on 2 levels of screening. First level screening; we screened titles and abstracts the following exclusion criteria: a) publications of case reports, letters, comments, and reviews not reporting original data; b) in vivo and/or in vitro studies; c) studies with fewer than 10 patients; and d) language other than English. Studies matching inclusion criteria were obtained in the complete form and reviewed in full-text version for an advance assessment.

Second level screening included a full-text screening that was performed using the following inclusion criteria: a) Original studies comparing sentinel node mapping and lymphadenectomy for the treatment of endometrial cancer, b) Studies that include at least 10 endometrial cancer patients for each arm, and c) Full text available in English.

2.4. Data extraction

Working independently, two reviewers (GB and FM) extracted the data using a piloted and standardized form. The following information was extracted: study design variables, patients' characteristics, surgical details of procedure, and surgery-related outcomes.

2.5. Outcomes

Mean outcome measures were positive node detection rate and survival outcomes (disease-free (DFS) and overall (OS) survivals). Other outcome measures included the following surgical related outcomes: mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate(s), in-hospital stay, postoperative complications and they were graded per the Accordion severity system [3].

Patients were classified as low-risk to have lymphatic spread according the Mayo Clinic classification system [3]. Basically, all patients with endometrioid FIGO grade 1 and 2 endometrial cancer confined in the inner half of the endometrium are classified as low risk endometrial cancer patients [3]; while all other patients were considered to have a high risk of having lymphatic disease.

2.6. Statistical analysis

Der-Simonian and Laird random-effects models were used to pool log transformed event rates and estimated 95% CI for dichotomous outcomes, and for continuous outcomes we calculated the weighted mean difference (MD) between the two interventions for each study and we

pooled the effect size using the same models [11]. Across the included studies was measured the overall heterogeneity using I^2 statistic, in which $I^2 > 50\%$ suggests high heterogeneity [11]. The meta-analysis was performed using the Cochrane Review software (Review Manager version 5.3 for Mac).

2.7. Methodological quality and risk of bias assessment

Cochrane Collaboration's Risk of Bias assessment tool was used to assess the quality of randomization methods, allocation concealment, baseline imbalances, whether blinding was done adequately and who was blinded [12].

The quality and levels of recommendation of the investigations were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) and American College of Obstetricians and Gynecologists guidelines (ACOG) guidelines, respectively [13,14]. ACOG categorize quality and quantity of evidence, underlying recommendations, in three levels: level A (good and consistent evidence), level B (limited or inconsistent evidence) and level C (consensus and opinion) [14].

3. Results

3.1. Evidence acquisition

Searching the Literature, we identified 395 citations. After the exclusion of non-English language literature, single arm studies, duplicate publications, case series including <10 laparoscopic procedures, letters, editorials and reviews not reporting original data, seven comparative series were selected [15–21]. One study was excluded [21] since it included overlapping data with another study [19], thus leaving six papers available for the analysis. The process of evidence acquisition is detailed in Fig. 1. Included studies were summarized the in Table 1. Overall, 3536 patients were included: 1249 (35.3%) and 2287 (64.7%), undergoing sentinel node mapping and lymphadenectomy, respectively.

3.2. Outcomes

Data about surgery-related outcomes are missing in all studies. Data regarding positive node detection rate was available in all six studies [15–20]. Looking at the ability of various method of nodal assessment in detecting positive pelvic nodes we observed that sentinel node mapping allowed a higher detection rate of patients with positive pelvic nodes than lymphadenectomy. Considering the whole population of low and high-risk endometrial cancer we observed that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03; (95%CI: 1.30 to 3.18); $p = 0.002$; and test for overall effect: $Z = 3.12$). No difference in detection of positive nodes located in the paraaortic are was observed comparing sentinel node mapping vs. lymphadenectomy (OR: 93 (95%CI: 0.39 to 2.18); $p = 0.86$; and test for overall effect: $Z = 0.18$). Fig. 2 reports forest plots regarding positive node detection rates into the pelvic and paraaortic area. Data regarding disease characteristics are reported in Table 2.

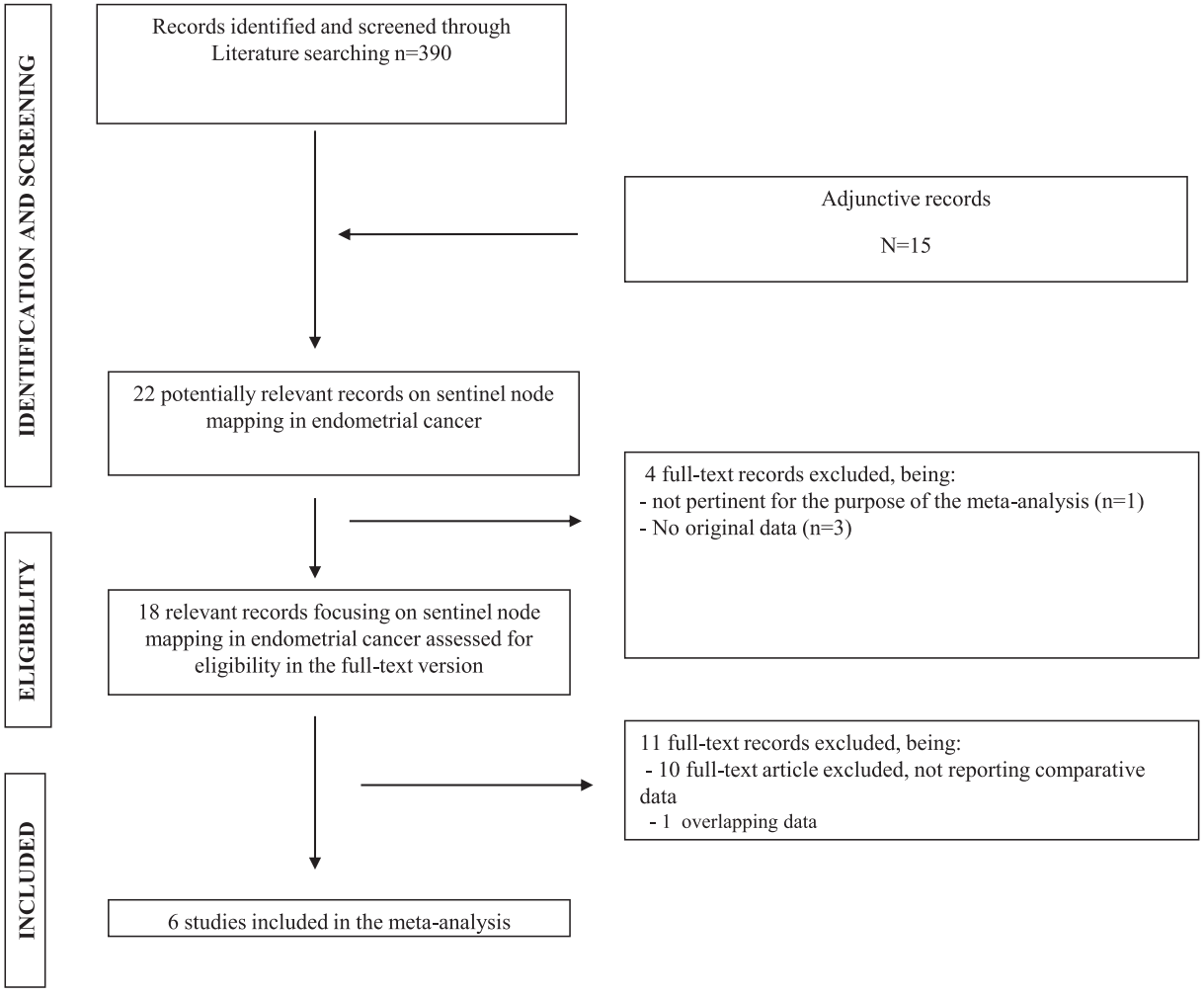

Fig. 1. PRIMA flow chart.

Table 1
Main characteristics of the included studies.

Authors	Year of publication	Principal institution(s) involved	Study design	Study period	Number of patients LND cohort	Number of patients SLN cohort	Level of recommendation for GRADE system	Level of evidence for ACOG guidelines
Eriksson A.G.Z. (a)	2015	Memorial Sloan Kettering Cancer Center, NY, USA; Mayo Clinic, Rochester, MN, USA	Retrospective	2004–2013	493	642	MQ	B
Holloway R.W.	2016	Florida Hospital Cancer Institute and Global Robotics Institute, Orlando, FL, USA	Retrospective	2006–2013	661	119	MQ	B
Baiocchi G.	2017	AC Camargo Cancer Center, Sao Paulo, Brazil	Retrospective	2007–2017	161	75	MQ	B
Buda A.	2017	San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy; Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy	Retrospective	NR	657	145	MQ	B
Ducie J.A. (a)	2017	Memorial Sloan Kettering Cancer Center, NY, USA; Mayo Clinic, Rochester, MN, USA	Retrospective	2004–2013	210	202	MQ	B
Buda A.	2018	San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy	Retrospective	NR	105	66	MQ	B

Abbreviation: LND, lymphadenectomy; SLN, sentinel node mapping; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; ACOG = American College of Obstetricians and Gynecologists; LQ = low quality; MQ = medium quality; HQ = high quality; NR = not reported; (a)lymphadenectomy was performed for any pts. in whom frozen section evaluation demonstrated grade 3 endometrioid or any non-endometrioid, >50% DOI, tumor > 2 cm at Mayo Clinic (cohort of lymphadenectomy, 2004–2008).

Considering low-risk endometrial cancer, patients having sentinel node mapping were more likely to be diagnosed with positive pelvic nodes in comparison with patients having lymphadenectomy (OR: 3.12 (95% CI: 1.32 to 7.39); $p = 0.01$); while number of positive paraaortic nodes was similar (OR: 1.38 (95% CI: 0.39 to 4.83); $p = 0.19$). This data is confirmed in the setting of intermediate and high-risk endometrial cancer: detection rate of positive pelvic nodes was higher in the sentinel node mapping group in comparison to the control group (OR: 2.04 (95% CI: 1.19 to 3.48); $p = 0.009$); while, detection of positive paraaortic nodes (OR: 0.94 (95% CI: 0.34 to 2.64); $p = 0.91$) was similar between groups.

Data on recurrence-free survival was available for three studies [15,18,20]. Data were available 2108 patients: including 853 (40.4%) and 1255 (59.6%) patients having sentinel node mapping and lymphadenectomy respectively. Fig. 3 shows the risk of developing recurrence (all sites) and lymphatic recurrence comparing patients having sentinel node mapping vs. patients having lymphadectomy. Overall recurrence rate (all sites) was 4.3% and 7.3% after sentinel node mapping

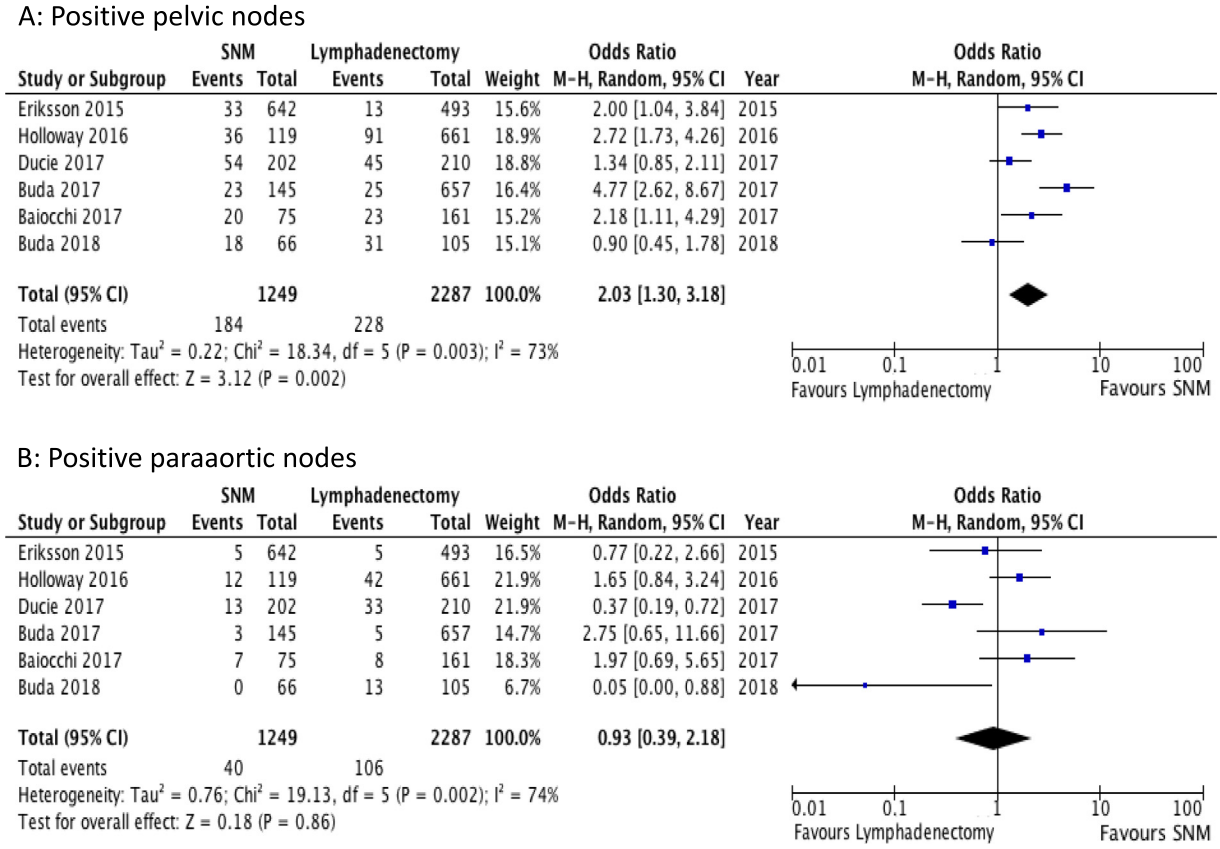

Fig. 2. Detection rate Ability of sentinel node mapping (SNM) and lymphadenectomy in identifying positive pelvic (A) and paraaortic (B) nodes.

Table 2
Disease characteristics.

Authors	Year of Publication	Principal institution(s) involved	Approach	Intermediate risk	High risk	Positive cytology	LVSI+	MI > 50%	Cervix stroma +	Positive pelvic nodes	Positive paraaortic nodes	Macrometastasis	Micrometastasis	Isolated tumor cells	Negative predictive value (NPV) and sensitivity of sentinel node mapping (h)
Eriksson A.G.Z.	2015	Memorial Sloan Kettering Cancer Center, NY, USA;	LND (n = 493)	NR	NR	30 (6.1%)	15 (3%)	0	3 (0.6%)	13/258 (11.23%) (b)	5/245 (2.0%) (c)	NR	NR	NR	//
		Mayo Clinic, Rochester, MN, USA	SLN (n = 642)	NR	NR	68 (10.6%)	94/617 (15.2%)	0	5 (0.8%)	33/596 (5.5%) (b)	5/93 (5.4%) (c)	11/36 (30.5%)	2/36 (5.5%)	23/36 (63.8%)	NR
Holloway R.W.	2016	Florida Hospital Cancer Institute and Global Robotics Institute, Orlando, FL, USA	LND (n = 661)	297 (44.9%) (d)	144 (21.8%) (d)	NR	192 (29.0%)	185 (28.0%)	NR	91 (13.7%)	42 (6.3%)	74 (11.2%)	17 (2.6%)	6 (0.9%)	//
			SLN (n = 119)	55 (46.2%) (d)	39 (32.8%) (d)	NR	40 (33.6%)	35 (29.2%)	NR	36 (30.3%) (e)	12 (10.1%)	14 (11.8%)	10 (8.4%)	12 (10.1%)	NPV = 98.8% Sensitivity = 97.2%
Baiocchi G.	2017	AC Camargo Cancer Center, Sao Paulo, Brazil	LND (n = 161)	0	161 (100%)	NR	25 (15.5%)	97 (60.2%)	NR	23 (14.3%)	8/142 (5.6%)	NR	NR	NR	//
			SLN (n = 75)	0	75 (100%)	NR	32 (42.7%)	43 (57.3%)	NR	20 (26.7%)	7/52 (13.5%)	8 (12.5%)	6 (9.4%)	4 (6.3%)	NPV = 95.7% Sensitivity = 90%
Buda A.	2017	San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy;	LND (n = 657)	179 (29.5%)	105 (17.3%)	NR	NR	NR	NR	25 (7.3%)	5 (0.8%)	86 (79.6%)	12 (12.2%)	//	//
		Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy	SLN (n = 145)	34 (23.6%)	39 (27.1%)	NR	NR	NR	NR	23 (16.7%)	3 (2.1%)	54 (81.8%)	8 (12.1%)	4 (6.1%)	NR
Ducie J.A.	2017	Memorial Sloan Kettering Cancer Center, NY, USA;	LND (n = 210)	107 (50.9%)	103 (49.1%)	43 (20.5%)	65 (30.9%)	NR	26 (12.4%)	45/189 (23.8%) (g)	33/178 (18.5%) (g)	NR	NR	NR	//
		Mayo Clinic, Rochester, MN, USA	SLN (n = 202)	82 (40.6%)	120 (59.4%)	32 (15.8%)	107 (53%)	NR	23 (11.4%)	54/198 (27.3%) (g)	13/84 (15.5%)(g)	35/55 (63.6%)	8/55 (14.5%)	12/55 (21.8%)	NR
Buda A.	2018	San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy	LND (n = 105)	//	105	NR	48 (46.1%)	52 (55.3%)	NR	31 (29.5%)	13/54 (24%)	40 (70.6%)	10 (19.2%)	2 (3.9%)	//
			SLN (n = 66)	//	66	NR	25 (40.3%)	26 (52.0%)	NR	18 (27.3%)	0 (0%)	11 (44%)	11 (44%)	3 (12%)	NR

Abbreviation: LND, lymphadenectomy; SLN, sentinel node mapping; LVSI, lymphovascular space invasion; MI, myometrial invasion; NR, not reported; (a) limited to patients with specified lymphadenectomy (b) positive pelvic nodes among patients undergoing pelvic LND (c)positive para-aortic nodes among patients undergoing para-aortic LND (d) according to GOG-99 risk stratification (e)35/36 the one false negative SLN resulted from bisecting a fusiform LN and including only the portion with dye. The portion without dye contained a macromestastasis (f) according to ESGO-ESMO-ESTRO (g) only includes cases in which nodal tissue was obtained (h) available for studies in which patients had sentinel node mapping followed by lymphadenectomy.

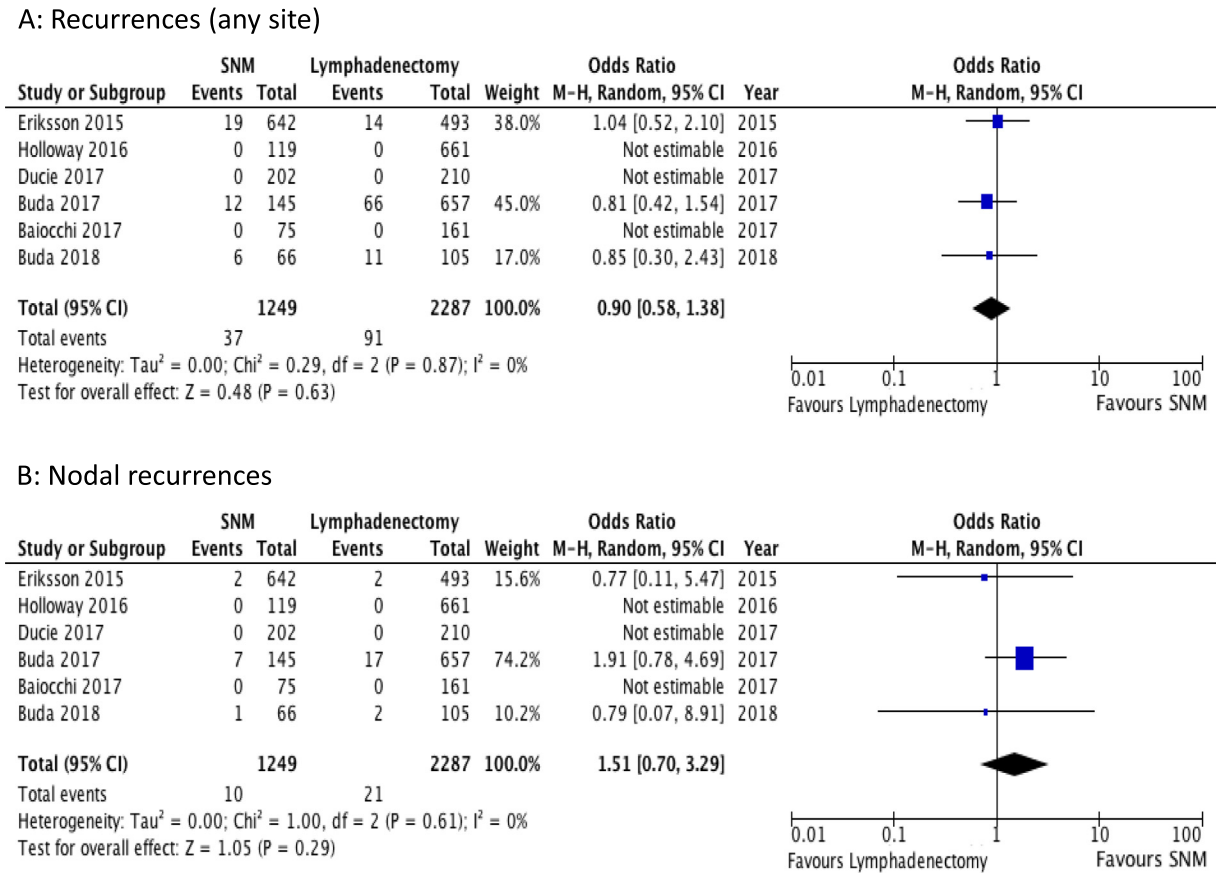

Fig. 3. Oncologic outcomes Prevalence of overall (A) and lymphatic specific (B) recurrences in patients having sentinel node mapping (SNM) and lymphadenectomy.

and lymphadenectomy, respectively. No statistical difference in recurrence-free rate was observe between groups (OR: 0.90 (95% CI: 0.58 to 1.38); $p = 0.63$; and test for overall effect: $Z = 0.48$). Similarly, if we focus on lymphatic recurrence we observed that nodal recurrences are statistically similar comparing sentinel node mapping and lymphadenectomy (1.2% vs. 1.7%; OR: 1.51 (95% CI: 0.70 to 3.29); $p = 0.29$; and test for overall effect: $Z = 1.05$). Table 3 reports oncologic outcomes.

3.3. Methodological quality and risk of bias assessment

All six studies included were retrospective studies [15–20]. The risk of allocation biases in the included studies was generally low for all six studies. Overall, there was a relatively high heterogeneity ($I^2 > 50\%$) in positive pelvic and paraaortic node detection rate; while no heterogeneity was observed focusing on recurrence rates (both for any site and nodal recurrence). Detailed risk of bias assessment is described in Supplemental Fig. 1.

4. Discussion

The present study investigated the current evidence on the role of sentinel node mapping in comparison to standard lymphadenectomy in endometrial cancer patients, thus observing a number of noteworthy findings. First we observed that the adopting sentinel node mapping achieves a higher detection rate of nodal disease in comparison to lymphadenectomy. Our data highlight that although this finding is more evident for patients at low risk of lymphatic dissemination, sentinel node mapping allows an accurate detection of positive nodes even in high-risk endometrial cancer. Additionally, these cumulative data support the non-inferiority of sentinel node mapping in comparison to lymphadenectomy in terms of oncologic outcomes. The prevalence of recurrence (any site) and lymphatic-specific recurrence is similar comparing the two methods of nodal assessment.

Sentinel lymph node mapping is rapidly gaining clinical acceptance for in endometrial cancer staging procedures. Accumulating data support that sentinel node mapping is effective and safe. In 2014, the NCCN guidelines first recognized the sentinel node mapping as an acceptable alternative to a lymphadenectomy in selected cases [7,8]. In 2018, the NCCN approved the execution of sentinel node mapping even in high-risk endometrial cancer patients, thus supporting the value that sentinel node mapping gained into clinical practice [7,8]. In fact, sentinel node mapping allows to identify patients with extrauterine disease reducing morbidity related to conventional lymphadenectomy. The omission of systematic lymphadenectomy would reduce the risk of surgery-related morbidity, including lymphatic-specific complications (i.e., lymphoceles, lymphorrhea and lymphedema) [7].

Accumulating data underlined that the execution of sentinel node mapping is the most cost-effective approach for nodal assessment in endometrial cancer patients. Suidan et al., investigated the cost-utility of three lymphadenectomy strategies (lymphadenectomy, selective lymphadenectomy based on frozen section criteria and sentinel node mapping) in the management of low-risk endometrial carcinoma [22]. Taking in to account type of surgical approach and lymphedema treatment costs ($2500/year). For the estimated women undergoing surgery for low-risk endometrial carcinoma each year in the United States (about 40,000 individuals), the annual cost of routine lymphadenectomy, selective lymphadenectomy, and sentinel lymph node mapping would be $722 million, $681 million, and $656 million, respectively [22]. Moreover, the authors observed that this latter has the highest quality-adjusted survival, making sentinel node mapping most cost-effective strategy in the management of low-risk endometrial carcinoma.

Table 3
Oncologic outcomes.

Authors	Year of Publication	Principal institution(s) involved	Approach	Recurrence	Nodal recurrence	Death of disease	Death for any cause	DFS at 5 yrs	OS at 5 yrs	Adjuvant	Follow-up
Eriksson A.G.Z. (a)	2015	Memorial Sloan Kettering Cancer Center, NY, USA;	LND (n = 493)	14 (2.8%)	2/14 (14.3%)	5 (1.0%)	15 (3.0%)	96.8%	95.4%	53 (10.7%)	3.5 yrs
		Mayo Clinic, Rochester, MN, USA	SLN (n = 642)	19 (3%)	2/19 (10.5%)	0 (0%)	9 (1.4%)	94.9%	97.4%	174 (27%)	2.1 yrs
Holloway R.W.	2016	Florida Hospital Cancer Institute and Global Robotics Institute, Orlando, FL, USA	LND (n = 661)	NR	NR	NR	NR	NR	NR	298 (45.1%)	NR
			SLN (n = 119)	NR	NR	NR	NR	NR	NR	60 (50.5%)	NR
Baiocchi G.	2017	AC Camargo Cancer Center, Sao Paulo, Brazil	LND (n = 161)	NR	NR	NR	NR	NR	NR	NR	NR
			SLN (n = 75)	NR	NR	NR	NR	NR	NR	NR	NR
Buda A. (a)	2017	San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy; Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy	LND (n = 657)	66 (11%)	17 (25.6%)	NR	7.8%-8.3% (b)	89.6%	NR	235 (35.7%)	34 (1–294) mo
			SLN (n = 145)	12 (8.4%)	7 (58.2%)	NR	4.5%	90.4%	NR	35 (24.1%)	30 (3–75) mo
Ducie J.A.	2017	Memorial Sloan Kettering Cancer Center, NY, USA;	LND (n = 210)	NR	NR	NR	NR	NR	NR	NR	NR
		Mayo Clinic, Rochester, MN, USA	SLN (n = 202)	NR	NR	NR	NR	NR	NR	NR	NR
Buda A.	2018	San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy	LND (n = 105)	9 (8.6%)	2 (1.9%)	NR	10 (9.5% (c)	81.6%	NR	80 (76.2%)	16 (6–88) mo
			SLN (n = 66)	6 (9.1%)	1 (1.5%)	NR	3 (4.5%) (c)	79.2%	NR	32 (48.5%)	30 (5–80) mo

Abbreviation: LND, lymphadenectomy; SLN, sentinel node mapping; DFS, disease-free survival; OS, overall survival; NR, not reported; yrs., years; mo, months. (a) at 3 yrs. (b) the death rate was 7.8% in pts. that did not underwent a LD, and 8.3% in women who had undergone to LND alone. (c) non specified if any death of disease.

Earlier studies focusing on sentinel node mapping aimed to show the non-inferiority of sentinel node mapping in comparison to lymphadenectomy [15–17,23–26]. However, they demonstrated that the adoption of sentinel node mapping is related to a more clear identification of patients with lymphatic dissemination [15–17]. In fact, pathological ultrastaging allows to identify low volume disease (i.e., micrometastasis and isolated tumor cells) not detectable via conventional pathological examination of nodes yielded. According to the classification of the AJCC, micrometastasis are classified as microscopic clusters and single neoplastic cells measuring >0.2 mm to ≤2 mm; isolated tumor cells are classified as microscopic clusters and single neoplastic cells measuring ≤0.2 mm [27]. Several experiences in the setting of sentinel node mapping suggested that low volume disease accounted in a relative high proportion of patients (more than one half of patients with lymphatic disease). Looking at the data of two prospective trials on sentinel node mapping (the FIRES and the FILM trials), we observed that low volume disease in sentinel nodes was 54% of patients with positive sentinel nodes in the FIRES and 62% of patients with positive sentinel nodes in the FILM trials [28,29]. In particular, this latter study among 21 positive sentinel node, macrometastatic disease was found in eight (38%) nodes, micrometastatic disease in five (24%), and isolated tumor cells in eight (38%) [29]. All these data highlight that low volume disease represents a non uncommon entity in endometrial cancer. Interestingly, there is a growing consensus suggesting that low volume disease is more common detected among patients at low risk of lymphatic spread; while high-risk patients are more likely to develop macrometastasis [30,31]. Our study corroborated this finding. In fact, looking at the ability to identify patients with positive nodes, sentinel node mapping seems to be non-inferior to lymphadenectomy. But focusing to low risk patients only, sentinel node mapping seems to be superior to standard lymphadenectomy. The inherent limitations of the retrospective nature of the studies included represent the main weakness of the present investigation. Whilst, the main merit include the collection of about 3500 endometrial cancer patients.

Another point deserving to be discussed is the detection of positive paraaortic nodes. Although our data underlined that detection of paraaortic nodes is similar between patients having sentinel node mapping and conventional lymphadenectomy, very few studies reported detection of sentinel nodes in the paraaortic area [10]. Then, owing to the paucity of data, the decision to dissect paraaortic lymph nodes likely depends on assessment of the uterine pathology and on the presence of gross pelvic nodes. Further studies aimed to assess the value of identifying paraaortic sentinel nodes in endometrial cancer are warranted.

In conclusion the present study investigated the role of sentinel node mapping in comparison to lymphadenectomy. We reviewed the current evidence, thus highlighting the safety and effectiveness of sentinel node mapping during endometrial cancer staging procedures. The adoption of sentinel node mapping would improve our ability to identify patients (especially low risk ones) with disease harboring in the lymph nodes, thus allowing to tailor adjuvant treatments. Further evidence focusing on the role of low volume disease is warranted. Moreover, owing to the low levels of evidence of the included studies, prospective randomized studies are needed in order to weight *pros and cons* of the widespread adoption of sentinel node mapping during endometrial cancer staging procedures.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.254.

Author contribution

Conceptualization: GB., Methodology: All authors.; Project administration: FR.; Supervision: FR.; writing - original draft: GB, AD, FM; writing - review & editing: all authors.

Conflicts of interest

The Authors declare no conflicts of interest. No funding sources supported this investigation.

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