Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature

M. Ansari[1], M.A. Ghodsi Rad[2], M. Hassanzadeh[3], H. Gholami[4], Z. Yousefi[3], V.R. Dabbagh[2], R. Sadeghi[2]

[1]Nuclear Medicine Department, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran
[2]Nuclear Medicine Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad
[3]Women's Health Research Center, Mashhad University of Medical Sciences, Mashhad
[4]Meta-analysis Sub-Committee, Evidence Based Medicine Committee, Mashhad University of Medical Sciences, Masshad (Iran)

Summary

Purpose: Sentinel lymph node biopsy is a fairly new approach for staging of gynecological malignancies. In the current study, the authors comprehensively reviewed the available reports on sentinel node biopsy of endometrial cancer. *Materials and Methods:* The authors searched Medline, SCOPUS, ISI web of knowledge, Science Direct, Springer, OVID SP, and Google Scholar with the following search terms: "endometrium OR endometrial OR uterine OR uterus AND sentinel". The outcomes of interest were detection rate and sensitivity. *Results:* Overall, 35 studies had enough information for false negative rate evaluation and 51 studies (including the sub-groups of individual studies) for detection rate evaluation (2,071 patients overall). Pooled detection rate was 77.8% (95% CI: 73.5-81.5%) and pooled sensitivity was 89% (95% CI: 83-93%). Cervical injection, as well as using both blue dye and radiotracer, results in higher detection rate and sensitivity. New techniques such as fluorescent dye injection and robotic-assisted surgery showed high detection rate and sensitivity. *Conclusion:* Sentinel node mapping is feasible in endometrial cancer. Using both blue dye and radiotracer and cervical injection of the mapping material can optimize the sensitivity and detection rate of this technique. Larger studies are still needed to evaluate the false negative rate and the factors influencing the sensitivity before considering this method safe.

Key words: Endometrial cancer; Sentinel node biopsy; Meta-analysis; Systematic review; False negative rate; Detection rate.

Introduction

Endometrial cancer is one of the most common female malignancies, which is expected to increase in frequency due to the recent surge of obesity (one of the major risk factors of this cancer) around the world [1, 2]. Lymph node involvement is one of the most important prognostic factors in the treatment of endometrial cancer and since 1988, FIGO has included pelvic and para-aortic lymphadenectomy during surgical staging of this malignancy [3]. However, the incidence of nodal metastasis is very low (about 10%) in early stage of endometrial cancer and routine lymphadenectomy would not be required in many of these patients [4]. Furthermore, lymphadenectomy imposes significant morbidity for the patients [5], and due to this fact, many centers do not perform it but reserve it for high-risk patients [6].

Sentinel lymph node biopsy is a fairly new approach for staging of gynecological malignancies [2]. In this method, only patients with pathologically proven sentinel lymph nodes (detected by gamma probe and/or blue dye during surgery) would undergo complete lymph node dissection. This approach can decrease the morbidity of the patients, while the accuracy of the lymph node staging would not be compromised.

Recently, results of several groups on sentinel node mapping of endometrial cancer have been published [7, 8] and many studies have been published on this topic in 2012.

In the current study, the authors comprehensively searched the available reports on sentinel node biopsy of endometrial cancer and summarized the results in the format of a systematic review and meta-analysis.

Materials and Methods

The authors searched Medline, SCOPUS, ISI web of knowledge, Science Direct, Springer, OVID SP, and Google Scholar with the following search terms: "endometrium OR endometrial OR uterine OR uterus) AND sentinel". Last search was done in March 2012. No language or date limitation was used for the present search strategy. If meeting the following inclusion criteria, meeting abstracts were also included. The reference lists of the primary studies, as well as citing articles, were searched separately for any other possible relevant study. The authors contacted the corresponding authors for more information when necessary.

Inclusion criteria

For evaluating the sensitivity of sentinel lymph node biopsy, only studies with the following criteria were included:

1) Using at least pelvic lymph node dissection (preferably para-aortic lymphadenectomy in addition) as the gold standard of lymph node involvement.

2) Total number of patients with positive lymph nodes, as well as those with false negative results (positive lymph nodes despite negative sentinel node) were both reported.

For evaluating the detection rate, only studies with the following criterion were included:

1) Total number of included patients, as well as those with detected sentinel nodes were both reported.

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Two authors independently reviewed the retrieved articles and any controversy regarding inclusion of the studies were resolved by the other author's opinion and consensus. Duplicate publications were discussed and only the most recent articles were included in the systematic review.

The quality of the retrieved studies was evaluated by the Oxford Center for Evidence Based Medicine Checklist of the diagnostic studies [9]. This checklist has several items including: consecutive patient recruiting, good spectrum of included patients (all eligible patients regardless of the severity or stage of the disease), independent evaluation of the index test regarding the results of the reference standard, the reference standard itself (should be the best available test which is pelvic (and para-aortic) lymph node dissection in the present systematic review), and sufficient explanation of the performed tests in order to insure reproducibility.

Data abstraction was performed independently by two authors and the following data were extracted from each study: authors, publication year, method of sentinel node mapping, bilateral lymphatic drainage, location of sentinel nodes, using of immunohistochemistry (IHC), characteristics of the patients, detection rate, and sensitivity.

Statistical analysis

Random effects model (Der-Simonian and Laird method [10]) was used for pooling detection and false negative rates across the studies having in mind the considerable heterogeneity of the included studies regarding the method and included patients. For statistical evaluation of heterogeneity, Cochrane Q test was used (p value less than 0.05 was considered statistically significant). I^2 index was used to quantify the extent of heterogeneity. This index shows the amount of the heterogeneity among the included studies which is not caused by sampling errors and is real [11]. Sub-group analysis was used for exploring the heterogeneity among studies regarding different variables such as injection site, injection material, etc.

Publication bias was graphically evaluated by funnel plots. Egger's regression method was used to statistically evaluate the asymmetry of funnel plots which represents the publication bias [12].

All statistical analyses were done using Meta-Analyst [13], and Meta-Disc (version 1.4) [14].

Results

Figure 1 shows the summary of the search process of the present study. Forty-six studies were included in the review (2,071 patients) [8, 15-59]. Eight studies had two subgroups of patients and were included in the review separately [8, 20, 26, 35, 39, 41, 50, 52]. Another study had three different subgroups [25]. Overall 35 studies had enough information for false negative rate evaluation and 51 studies (including the sub-groups of the above-mentioned studies) for detection rate evaluation. Quality assessment and summary data of the included studies are shown in Tables 1 and 2, respectively.

Detection rate

Figure 2 shows the forest plot of the detection rate pooling. Pooled detection rate was 77.8% [95% CI: 73.5-81.5%]. Cochrane Q value was 132.3 ($p < 0.0001$) and I^2 index was 61.4%.

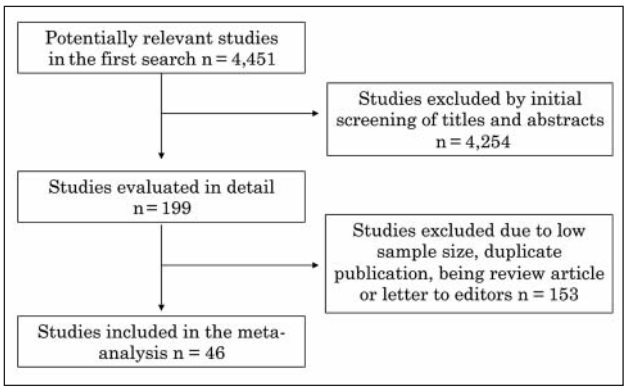

Figure 1. — Summary of the review process and inclusion of the studies.

Funnel plot of the detection rate pooling is shown in Figure 3. Egger's regression intercept was - 0.08 ($p = 0.84$).

Sub-group analyses regarding injection site showed 84.9% [78.8-89.4%], 73.9% [63.9-81.9%], 69.7% [57.7-79.4%], 86.1% [66.3-95.1%], and 50% [9-91%] detection rates for cervical, sub-endometrial, subserosal, cervical/subserosal, and sub-endometrial/subserosal injections respectively.

Considering the method of sentinel node mapping, the following results were obtained: 71.1% [62.6-78.3%], 76.7% [67-84.2%], and 82.8% [76.4-87.8%] detection rates for blue dye, tracer, and blue dye/tracer techniques respectively. Rossi *et al.* [54] and Holloway *et al.* [56] used florescent dye and near infra-red imaging for detection of the sentinel nodes with pooled detection rate of 94.2% [64.7-99.3%].

Finally, the effect of surgery type was evaluated and the following detection rates were obtained: 73.8% [65.1-81%], 76% [68.5-82.2%], and 88.5% [72-95.8%] for laparoscopy, laparotomy, and robotic assisted surgeries, respectively.

Sensitivity

Figure 4 shows the forest plot of the sensitivity pooling. Pooled sensitivity was 89% [83-93%]. Cochrane Q value was 31.97 ($p = 0.74$ and $I^2 = 0\%$).

Funnel plot of the sensitivity pooling is shown in Figure 5. Egger's regression intercept was - 0.02 ($p = 0.95$).

Subgroup analysis for injection site showed the following sensitivities: 89% [82-94%], 91% [79-98%], 84% [60-97%], and 100% [29-100%] for cervical, sub-endometrial, sub-serosal, and cervical/subserosal injections, respectively.

Considering the method of sentinel node mapping, the following pooled sensitivities were obtained: 86% [75-93%], 85% [69-95%], 93% [85-97%] for blue dye, tracer, and blue dye/tracer methods, respectively.

Sub-group analysis for type of surgery showed the following pooled sensitivities: 87% [74-95%], and 93% [77-99%] for laparotomy and laparoscopic surgeries, respectively.

Table 1. — *Quality assessment of the included studies.*

First author	Institution	Publication year	Consecutive recruitment	Prospective design	Gold standard	Enough explanation
Burk *et al.*	US (Houston)	1996	N/A	Yes	Pelvic and para-aortic lymphadenectomy	Yes
Echt *et al.*	US (New Orlean)	1999	Yes	Yes	Pelvic and para-aortic lymphadenectomy	Yes
Holub *et al.*	Czech Republic (Klando)	2001	Yes	Yes	Pelvic lymphadenectomy	Yes
Holub *et al.*	Czech Republic (Klando)	2002	Yes	Yes	Pelvic lymphadenectomy	Yes
Pelosi *et al.*	Italy (Torino)	2002	Yes	Yes	Pelvic lymphadenectomy	Yes
Pitynski *et al.*	Poland (Krakow)	2003	N/A	N/A	Pelvic lymphadenectomy and para-aortic in selected cases	Yes
Pelosi *et al.*	Italy (Torino)	2003	Yes	Yes	Pelvic lymphadenectomy	Yes
Holub *et al.*	Czech Republic (Klando)	2004	Yes	Yes	Pelvic lymphadenectomy (infra-aortic lymphadenectomy only in 1)	Yes
Fersis *et al.*	Germany (Teubingen)	2004	Yes	Yes	Pelvic lymphadenectomy (and para-aortic in selected cases)	Yes
Niikura *et al.*	Japan (Sendai)	2004	Yes	Yes	Pelvic and paraaortic lymphadenectomy	Yes
Gien *et al.*	UK (London)	2005	No (only patients with high risk of metastasis were included)	Yes	Pelvic lymphadenectomy/ Para-aortic in high risk patients (papillary serous and clear cell carcinomas)	Yes
Dzvincuk *et al.*	Czech Republic (Olomouc)	2006	Yes	Yes	Pelvic lymphadenectomy and para-aortic lymphadenectomy in 11 patients	Yes
Niccoli A. *et al.*	Italy (Bari)	2006	N/A	N/A	N/A	No
Lopes *et al.*	Brazil (Sao Paulo)	2007	Yes	Yes	Pelvic and para-aortic lymphadenectomy up to the level of the renal veins	Yes
Yan *et al.*	China (Foshan)	2007	Yes	Yes	Pelvic lymph node dissection	Yes
Altgassen *et al.*	Germany (Leubeck)	2007	No	Yes	Pelvic and para-aortic lymphadenectomy 15; pelvic 8	Yes
Delaloye *et al.*	Switzerland (Lausanne)	2007	N/A	Yes	Pelvic and para-aortic lymphadenectomy	Yes
Frumovitz *et al.*	US (Houston)	2007	No	Yes	Pelvic and para-aortic lymphadenectomy	Yes
Maccauro *et al.*	Italy (Milan)	2007	Yes	Yes	Pelvic lymphadenectomy and para-aortic in serous or papillary carcinomas	Yes
Jiang *et al.*	China (Sun Yat-sen)	2008	Yes	Yes	Pelvic lymphadenectomy	Yes
Bats *et al.*	France (Paris)	2008	Yes	Yes	Pelvic lymphadenectomy/para-aortic in selected cases	Yes
Clement *et al.*	France (Paris)	2008	No	Yes	Pelvic lymphadenectomy/para-aortic in selected cases	Yes
Ballester *et al.*	France (Paris)	2008	Yes	Yes	Pelvic lymphadenectomy (40) para-aortic in selected cases (6) (patients with clear cell or serous cancers)	Yes
Perrone *et al.*	Italy (Bologna)	2008	Yes	Yes	Pelvic lymphadenectomy and lombo-aortic lymphadenectomy was performed in high grade EC and in cases of lombo-aortic captation of SLN	Yes
Li *et al.*	China (Bejing)	2009	N/A	Yes	Pelvic lymphadenectomy in 27 patients/pelvic node sampling in 4/7 of the 31 patients, a para-aortic lymph node sampling was performed	Yes
Robova *et al.*	Czech Republic (Prague)	2009	N/A	Yes	Pelvic and para-aortic lymphadenectomy up to the inferior mesenteric artery	Yes
Vidal-Sicart *et al.*	Spain (Barcelona)	2009	N/A	Yes	Selected lymphadenectomy	Yes
Kara *et al.*	Turkey (Ankara)	2009	Yes	Yes	Pelvic and para-aortic lymphadenectomy	Yes
Zenzola *et al.*	Venezuela (Caracas)	2009	Yes	Yes	Pelvic lymphadenectomy	Yes
Gemignani *et al.*	US (New York)	2009	Yes	Yes	Pelvic lymphadenectomy in all and pelvic as well as para-aortic in some at the surgeons discreption	Yes
Qu *et al.*	China (Shandong)	2010	Yes	Yes	Pelvic and para-aortic lymphadenectomy	Yes
Feranec *et al.*	Czeck Republic (Brno)	2010	Yes	Yes	Pelvic lymphadenectomy (para-aortic in high risk patients)	Yes
Dittmann *et al.*	Germany (Teubingen)	2010	N/A	Yes	N/A	No
Sola *et al.*	Spain (Barcelona)	2010	Yes	Yes	Regional lymph node dissection	No
Mais *et al.*	Italy (Cagliari)	2010	Yes	Yes	Pelvic lymphadenectomy	Yes
Ballester *et al.*	France (Multicenter)	2011	Yes	Yes	Pelvic lymphadenectomy and para-aortic lymphadenectomy in 15 patients	Yes
Cordero García *et al.*	Spain (Madrid)	2012	Yes	Yes	Pelvic lymphadenectomy	Yes
Barlin *et al.*	US (New York)	2012	Yes	Yes	Pelvic lymphadenectomy in all and pelvic as well as para-aortic in some at the surgeons discretion	Yes
Leitao *et al.*	US (New York)	2011	Yes	Yes	Pelvic lymphadenectomy in all and pelvic as well as para-aortic in some at the surgeons discretion	No
Rossi *et al.*	US (Indiana)	2012	N/A	Yes	Pelvic lymphadenectomy and para-aortic lymphadenectomy	Yes
Holloway *et al.*	US (Orlando)	2012	N/A	No	Pelvic lymphadenectomy in all and para-aortic lymphadenectomy in high risk patients	Yes
Buda *et al.*	Italy (Monza)	2012	Yes	Yes	Pelvic lymphadenectomy in all and para-aortic lymphadenectomy in selected patients	Yes
How *et al.*	Canada (Montreal)	2012	Yes	Yes	Pelvic lymphadenectomy in all and para-aortic lymphadenectomy in selected patients	Yes
Solima *et al.*	Italy (Milan)	2012	Yes	Yes	Pelvic lymphadenectomy in all and para-aortic lymphadenectomy in high risk patients	Yes

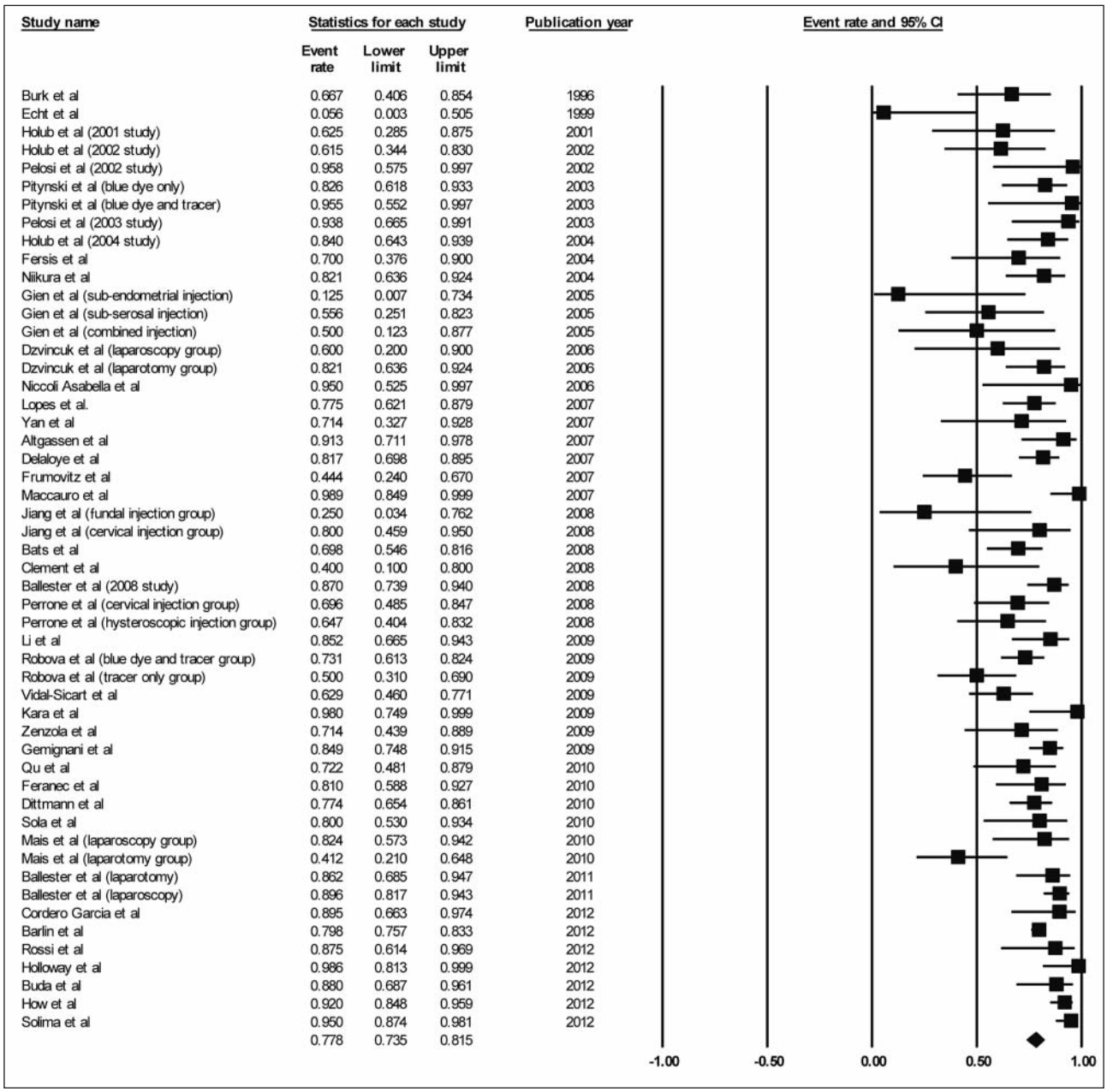

Figure 2. — Forrest plot of the detection pooling rate.

Rossi *et al.* [54], Holloway *et al.* [56], and How *et al.* [58] used robotic-assisted surgery with florescent dye with pooled sensitivity of 86% [64-97%].

Including only larger studies with more than five patients with positive lymph nodes showed pooled sensitivity of 89% [83-94%].

Discussion

Sentinel node biopsy is a novel method for regional lymph node staging of many solid tumors including breast cancer [60], urological malignancies [61], etc. This method can considerably decrease the morbidity of regional lymph node dissection by sparing many patients of this invasive procedure [62]. This concept had been used for endometrial cancer since 1996 [15] with different results. In the current systematic review, the authors comprehensively searched and pooled results of available studies.

In should be mentioned that in 2011, similar systematic review was published by Kang *et al.* [63]. The present systematic review had considerable more complete search strategy as the authors could locate 46 relevant studies compared to Kang *et al.* This systematic review also included the most recent results of the most experienced

group in sentinel node mapping of endometrial cancer (Barlin *et al.* study [53]) which makes it more valid. In addition, Kang *et al.* study had several errors in data extraction: for example they considered articles by Holub *et al.* [17, 18, 22] as duplicate and did not include two of them in the analysis. However these three studies are methodologically different and the authors included them in this study. Finally, sensitivities of Delaloye *et al.* [31] and Burk *et al.* [15] studies were mistakenly calculated by Kang *et al.*: 89% and 50%, despite being 100% and 67%.

Detection rate

Pooled detection rate was rather low (77.8%) compared to other malignancies such as breast cancer. However the included studies were highly heterogeneous ($I^2 = 61.4\%$) and subgroup analysis showed that injection site, and mapping method could affect detection rate. For example Echt *et al.* reported 0% detection rate in their study, which could be attributed to the intramyometrial injection of the tracer as they mentioned themselves [16]. As shown above, cervical or combined cervical/subserosal injections of the tracer had the highest detection rates compared to other techniques such as sub-endometrial or subserosal. This can be due to ease of cervical injection compared to other sites [64].

Using both blue dye and radiotracer showed the highest detection rate compared to either of the methods alone. Fluorescent dye (using near infrared imaging intraoperatively) was used in two studies with very high detection rate and seems to be a promising method.

Unilateral and bilateral mapping

Endometrium as a midline organ has two different pathways of lymphatic drainage: right and left [8]. As shown in Table 2, the rate of bilateral drainage was not reported in many studies included in the current meta-analysis. This rate was between 97.1% in Holloway *et al.* study [56] and 12.5% in Frumovitz *et al.* study [32]. In the two largest series, this rate was 69% [8] and 63% [53], respectively. Failure to detect sentinel nodes bilaterally can be of importance regarding the need to perform lymphadenectomy on the failure side. Two of the largest studies thus far have evaluated this notion in detail. Ballester *et al.* reported 100% sensitivity while using hemipelves as the unit of calculations despite 84% using patients as the unit [8]. Barlin *et al.* also showed the same results as they reported 98.1% sensitivity using hemipelves as the unit of calculations despite 85.1% using the patients as the unit [53]. It is worth mentioning that for other midline organs such as the penis, this method has been used with fairly promising results [65].

Distribution of sentinel nodes and para-aortic sentinel lymph nodes

As shown in Table 2, distribution of sentinel nodes depends on the injection site of the mapping materials. The sub-serosal and sub-endometrial methods show para-aortic sentinel nodes more frequently (as high as 38% of all sentinel nodes in one study) [15]. Isolated para-aortic sentinel node detection was also reported in 1%-36% of patients in various studies [23, 24, 32, 40, 53, 58, 59].

Para-aortic lymph node dissection is under much debate in endometrial cancer. The incidence of para-aortic lymph node metastasis without pelvic lymph node involvement was reported to be 1% [66]. The incidence of isolated para-aortic recurrence was also reported to be only 6%, most of which were in grade 3 tumors. The present meta-analysis also supports these data since positive para-aortic sentinel nodes were only reported by limited studies: Lopes *et al.* (four out of five patients with positive nodes) [28], Feranec *et al.* (one patient which was the only positive patient) [47], Fersis *et al.* (one patient in both para-aortic and pelvic regions), Delaloye *et al.* (in 40% of positive sentinel nodes) [31], Maccauro *et al.* (one out of seven positive patients) [33], Niikura *et al.* (one out of six positive patients) [67], Holloway *et al.* (five out of ten positive patients) [56], and Solima *et al.* (one out of ten positive patients) [59].

Altogether, it seems that the incidence of para-aortic lymph node involvement is low and cervical injection (which is very easy to perform) of the mapping material would suffice for sentinel node mapping.

Sensitivity

Overall, the pooled sensitivity of sentinel node mapping was 89% [83-93], which is fairly acceptable compared to other known malignancies, such as breast cancer or melanoma [68]. The included studies were not that heterogeneous in this regard (Cochrane Q value = 31.9, $p = 0.7$ and $I^2 = 0\%$).

Sub-group analysis showed that using both blue dye and tracer had the highest sensitivity compared to either technique alone. This was in accordance with other malignancies such as breast and urological cancers [61, 68].

Site of injection and type of surgery were both related to sensitivity: laparoscopic surgery and cervical/subserosal injection showed higher pooled sensitivities.

Effect of immunohistochemistry (IHC)

High frequency of lymph node micro-metastasis has been reported to occur in endometrial cancer, however detection of micro-metastases by routine IHC evaluation of all removed lymph nodes is not time or cost-effective [69]. However, using IHC on the removed sentinel nodes seems to be cost-effective and can decrease the false negative rate. This was supported by the results of the present meta-analysis. Lopes *et al.* [28], Bats *et al.* [36], Ballester *et al.* [38], Ballester *et al.* (multicenter study)[8], Altgassen *et al.* [30], Kara *et al.* [43], Perrone *et al.* [39], Niikura *et al.* [24], Barlin *et al.* [53], Holloway *et al.* [56], and Solima *et al.* [59] reported 5, 2, 4, 9, 3, 1, 5, 4, 9, 4, and six additional positive nodes using IHC compared to the conventional hematoxylin and eosin (H&E) staining.

Although using IHC can decrease the false negative rate, however the prognostic impact of micro-metastasis is not yet clear and needs further studies with high sample size and long follow up [69].

Table 2. — *Summary of the included studies information.*

First author	Year	No. of patients	No. of patients with detected SN	No. of patients with posit. pelvic	No. of patients with positive SN	Blue dye			Radiotracer			Mean age	Grade	Stage	SLN distribution	No. of patients with bilateral drainage	Type of surgery	No. of positive node using IHC	Imaging	Comments
						Type	Injection site	Volume	Type	Injection site	Dose (in MBq)									
Burke *et al.*	1996	15	10	3	2	IB	SS	3 ml	N/A	N/A	N/A	N/A	G2 7; G3 2	N/A	Para-aortic sites in 12, common iliac in 6, and pelvic in 13	N/A	LP	N/A	N/A	Only patients with high risk of metastasis were included (G2 or 3 or variant histology).
Echt *et al.*	1999	8	0	N/A	N/A	IB	SE	2 ml	N/A	N/A	N/A	N/A	N/A	IB 7; IV 1	No detection	No SLN	LP	N/A	N/A	The injection was intramyometrial
Holub *et al.*	2001	8	5	1	1	PB	SE	2 ml	N/A	N/A	N/A	58.5	G1 1; G2 5; G3 2	Stage: IA-1, IB-5, IC-1, IIIC-1	Obturator, internal and common iliac / No para-aortic	5	LPS	N/A	N/A	
Holub *et al.*	2002	13	8	1	1	PB	SS	2 mll	N/A	N/A	N/A	59.8	N/A	Ia 2; Ib 6; Ic 4; IIIc 1	N/A	N/A	LPS	N/A	N/A	Only the subserosal group was included
Pelosi *et al.*	2002	11	11	N/A	N/A	PB	C	4 ml/ in 4 deposits	NC	C	37/ (0.4 ml) in 4 deposits (from another study of the group)	N/A	N/A	Ib 10; Iia 1	All internal iliac	6	LPS	N/A	Static imaging	
Pitynski *et al.*	2003	33	29	2	2	PB	SS and C	4 ml/ and 3 mL SS	NC (in 10 cases)	C	100	N/A	N/A	All Stage I	N/A	N/A	LP	Planar 2 hours post injection		Detection rate for the patients injected with tracer and blue dye both was 100% (10/10) and for those injected with blue dye only was 19/23
Pelosi *et al.*	2003	16	15	3	3	PB	c	4 ml/ in 4 deposits	NC	C	37 (0.4 ml) /in 4 deposits (from another study of the group)	63	N/A	Ib	All Internal iliac	9	LPS	N/A (however all were micro-metastases)	Static imaging	Lymphoscintigraphy showed SLNs in 15 patients
Holub *et al.*	2004	25	21	2	2	PB	SS and C	5 or 10 ml (4 or 9 ml in C) (four injections) and remaining in the midline SS	N/A	N/A	N/A	59.7	N/A	All Stage I	52.8% (28 of 53 lymph nodes) at the fossa obturatoria and internal iliac sites, in 13.2% (7 of 53 lymph nodes) at the division of the common iliac artery. In 34% in other pelvic areas. No para-aortic.	17	LPS	N/A	N/A	
Fersis *et al.*	2004	10	7 (in two patients SLN could be found retrospec-tively)	1	1	N/A	N/A	N/A	NC	SE	40-100	60	G1 2; G2 7; G3 1	N/A aortic 2	Interiliac 2; anterior parametrial tissue 2; para-aortic only 1; pelvic and para-	5	LP (LPS in 2)	N/A	Planar	

following Table 2. — *Summary of the included studies information.*

First author	Year	No. of patients	No. of patients with detected SN	No. of patients with posit. pelvic	No. of patients with positive SN	Blue dye			Radiotracer			Mean age	Grade	Stage	SLN distribution	No. of patients with bilateral drainage	Type of surgery	No. of positive node using IHC	Imaging	Comments
						Type	Injection site	Volume	Type	Injection site	Dose (in MBq)									
Niikura *et al.*	2004	28	23	6	5	N/A	N/A	N/A	P	SE	38-70/ 2 ml	56 (median)	G1 30; G2 8; G3 2	IA 7; IB 16; IC 9; IIA 3; IIB 1; IIIA 2; IIIC 2	Pelvic 6; Para-aortic 8; Both basins 22	8 out of 23	LP	4 out of 6	Dynamic imaging 10 min/ another spot the next day	Another study of this group [34] was also used for false negative rate which had overlap in 7 patients, however in the second study on 2007 detection rate cannot be determined due to excluding patients without SLN detection
Gien *et al.*	2005	16	8	1	0	IB	SS in 9; SE in 3; Both in 4	5-10 ml	N/A	N/A	N/A	N/A	G2 1; G3 2	N/A	Common iliac 3; External iliac 11; Obturator 2; Presacral 1	1	LP	N/A	N/A	Detection rate: 0/3 for subendometrial; Subserousal 5/9; Both 2/4
Dzvincuk *et al.*	2006	33	26 (3 in LPS and 23 in LP group)	3 (2 in LP pts)	3	N/A	N/A	N/A	NC	SE	50/2.5cc in 4-6 portion	62.3	GI 19; G2 6; G3 7; 1 patient not available	IA 5; IB 10 IC 3; IIA 3; IIB 6; IIIA 1; IIIC 5	All pelvic and 11 paraaortic	17	LP/ LPS in 5	N/A	Planar 20-90 post injection	Imaging was negative in 16 patients but SLN was found in 1 and vice versa in 1 patients
Niccoli Asabella *et al.*	2006	9	9	0	0	N/A	N/A	N/A	NC	SE	111 / 4 ml	56	N/A	N/A	3 external iliac nodes, 7 internal iliac nodes, 2 in the para-aortic area and 1 in common iliac site	N/A	LP	No positive SLN	Dynamic and static images at 20-30 and 120 minutes post injection	
Lopes *et al.*	2007	40	31	6	5	PB	SS	3 ml	N/A	N/A	N/A	64.2	Grade 1: 6, Grade 2: 27, Grade 3: 2,5 unknown	N/A	4 in the para-aortic, 3 in the pelvic region, and 4 in both regions.	N/A	LP	5 out of 11 positive patients		In 9 cases with detection failure 5 had lymph node metastases
Yan *et al.*	2007	7	5	1	1	MB	c	4 ml in 4 points	N/A	N/A	N/A	53 (median)	G2 in 4 and G3 in 3	IB 1, IC 1, IIIA 2, IIIC 3	N/A	N/A	LPS 5 and LP 2	N/A	N/A	Both failures in Stage IIIC
Altgassen *et al.*	2007	23	21	3 (5 with IHC)	2 (4 with IHC)	PB	SS	4 ml/in 8	N/A	N/A	N/A	64.7		I 16; II 9	49 pelvic; 6 para-aortic; 1 presacral	N/A	LP	3	N/A	The information of IHC is from the another study of this group [62]
Delaloye *et al.*	2007	60	49	8	8	PB	SE	2 ml	NC	SE	Activity variable (30 in 26 patients)	65 (median)	G1 22; G2 25; G3 13	IA 12; IB 22; IC 5; IIA 2; IIB 5; IIIA 6; IIIC 9	Pelvic 33; both pelvic and para-aortic 16	N/A	LP 47; LPS 13	N/A	No imaging	All 11 failures occurred during learning curve phase; tracer alone 15, blue dye alone 1 and both 33
Frumovitz *et al.*	2007	18	8	0	0	IB	SS	3 ml/ in 3 portions	FSC	SS	18.5-37/ 3 portions	67	G1 1; G2 9; G3 6; Malignant mixed; Müllerian tumor 2	IA 2; IB 7; IC 2; IIA 1; IIIA 1; IIIB 2	4 only in the pelvis, 2 in the pelvis and above the bifurcation of the aorta; 2 patients above the bifurcation of the aorta only	1	LP	N/A	Portable gamma camera was used in the first 10 pts without any yield	

following Table 2. — *Summary of the included studies information.*

First author	Year	No. of patients	No. of patients with detected SN	No. of patients with posit. pelvic	No. of patients with positive SN	Blue dye			Radiotracer			Mean age	Grade	Stage	SLN distribution	No. of patients with bilateral drainage	Type of surgery	No. of positive node using IHC	Imaging	Comments
						Type	Injection site	Volume	Type	Injection site	Dose (in MBq)									
Maccauro *et al.*	2007	45	45	7	7	PB	SE	8 ml/ portions	NC	SE	111	54	N/A	N/A	Common iliac 17; external iliac 16; internal iliac; obturatur 12; para-aortic 14 (from another study of this group)	N/A	LP	N/A	Dynamic for 15 min and statis views every 5 minutes for 1 hour	Only 38% blue nodes/ No blue-cold node
Jiang *et al.*	2008	4	1	0	0	MB	SS	4 ml	N/A	N/A	N/A	54.9	G1 11; G2 3	I:12; II:1; III: 1	Obturator 11; External iliac 4; Internal iliac 2	5	LPS	0	N/A	Fundal injection group
Jiang *et al.*	2008	10	8	0	0	MB	C	4 ml in 4 deposits	N/A	N/A	N/A			N/A			LPS	0		Cervical injection group
Bats *et al.*	2008	43	30	8	8	PB	C	2 ml/in four aliquotes	RSC	C	120 /in 4 aliquots	67.8	N/A	IA: 3 IB: 14 IC: 9 IIA: 3 IIB: 3	Interiliac 71; Common iliac 9; Promontory 6; No para-aortic	16	LPS	2	Planar 12 h post injection	In three patients sentinel node was detected by blue dye only
Clement *et al.*	2008	5	2	1	1	PB	SE in 4 and C in 1	2 ml/in four aliquotes	RSC	SE	120 /in 4 aliquots	N/A	N/A	IIIA: 1 IIIC: 10 N/A	Common iliac 2 external iliac 1 para-aortic 1	0	LPS		Planar 12 h post injection	In 1 patient blue dye only and in another one radiotracer only detected the SLNs
Ballester *et al.*	2008	46	40	10	10	PB	C	2 ml/in 2 aliqouts	USC	C	80/in 4 aliquots (0.2 ml each)	65	G1 27; G2 10; G3 3; NP 6	IA 7; IB 13; C 5; II 2; I IIIC 9	External iliac (lateral group), the iliac vessel bifurcation, the common iliac and the aortic bifurcation in 78 (78%), 16 (16%), 6 cases (6%) and 1 case (1%), No para-aortic	25	LPS 42 LP4	4	Planar 2 h post injection and then every 30 minutes	A total of 101 SN were removed. The SNs were blue and radioactive, radioactive alone and blue alone in 59, 33, and 9 cases, respectively.
Perrone *et al.*	2008	23	16	4	4	N/A	N/A	N/A	NC	C	55-74 /4 ml	63.4	G1 10; G2 7; G3 5	Stage I or II	Iliac region 15; obturator 1	6	LPS	4	Dynamic and static imaging 15 and 30 minutes post injection	Cervical injection group/imaging showed SLN in 20 patients
Perrone *et al.*	2008	17	11	2	2	N/A	N/A	N/A	NC	SE	110 /4 ml	68.6	G1 7; G2 6; G3 4	Stage I or II	Iliac region 10; obturator 1; aortic 2	3	LPS	1	Dynamic and static imaging 15 and 30 minutes post injection	Hysteroscopic injection group/imaging showed SLN in 10 patients

following table 2. — *Summary of the included studies information.*

First author	Year	No. of patients	No. of patients with detected SN	No. of patients with posit. pelvic	No. of patients with positive SN	Blue dye			Radiotracer			Mean age	Grade	Stage	SLN distribution	No. of patients with bilateral drainage	Type of surgery	No. of positive node using IHC	Imaging	Comments
						Type	Injection site	Volume	Type	Injection site	Dose (in MBq)									
Li *et al.*	2009	27	23	2	2	MB	SS	4 ml in 3 (stage I) or 2 (stage II) aliquots	N/A	N/A	N/A	53 (median)	G1 in 13 G2 in 12 and G3 in 6	IA 5; IB 8; IC 4; IIA 5; IIB 4; IIIA 2; IIIC 3	1 para-aortic 22 pelvic		LP	N/A		The first 4 patients were excluded due to defective injection
Robova *et al.*	2009	67	49	3	3	PB	SS	2 ml	HSA	SS	20 /2 ml	59.2 (median)	Grade 1 55 2 26 3 10	IA 9 IB 48 IC 19 IIA 7 IIB 3 IIIB 5	11/134 SLNs in the para-aortic area	41	LP	N/A	No imaging	
Robova *et al.*	2009	24	12			N/A	N/A	N/A	HSA	SE	40/2 ml								Planar 1 hour post injection	
Vidal-Sicart *et al.*	2009	35	22	3	1	N/A	N/A	N/A	NC	SE	148 /8 ml (in 17 patients 111 /2-4 ml)	65	N/A	Stage I or II	Parametrial (0%), obturator fossa (26%), external iliac region (32%), internal iliac (10%), primitive iliac (25%)and paraortic zone (20%).	39%	LPS	N/A and 2 h post injection	Planar 30 min metastasis	Only patients with middle-high risk of were included
Kara *et al.*	2009	24	24	3	2	N/A	N/A	N/A	NC	C	74 /4 doses	54 (median)		IA 4; IB 7; IC 6; IIA 7	Pelvic 19 (obturatur and external iliac in 74%) and pelvic and para-aortic in 5	11	LP	1	Dynamic (40 frames of 20 s) and static (500,000 counts) for 4 hours in anterior projection.	
Zenzola *et al.*	2009	14	10	1	1	PB	C	0.5 ml/in 4 deposits	SC	C	37 /in 2 deposits	65	G1 6; G2 5; G3 2	Ia 6; Ib 4; Ic 4	Right external iliac 6; Left external iliac 2; Right internal iliac 1; Left obturator 1	0	LP	N/A	Planar 20-30 post-injection	All SLN were hot, 3 blue/four failures were in the first patients.
Gemignani *et al.*	2009	73	62	10	8	IB or MB	C	4 ml (2 ml deep, 2 ml superficial)	FSC	C	37-148 /0.5-1 ml	N/A	N/A	N/A	N/A	N/A	LPS 42, LP 31	N/A	Dynamic imaging for 10 min (1 min per view) and static in 60 minutes/SPECT in 40 patients	Lymphoscintigraphy could detect sentinel nodes in 53 patients
Qu *et al.*	2010	18	13	2	2	MB	SS	4 ml in 4 deposits	N/A	N/A	N/A	56 (median)	G1 8; G2 4; G3 3	N/A	Internal iliac 11, external iliac 9, common iliac 7, obturator 18, abdominal aorta 2 (total 47)	N/A	LP	N/A	N/A	

following table 2. — *Summary of the included studies information.*

First author	Year	No. of patients	No. of patients with detected SN	No. of patients with post. pelvic	No. of patients with positive SN	Blue dye			Radiotracer			Mean age	Grade	Stage	SLN distribution	No. of patients with bilateral drainage	Type of surgery	No. of positive node using IHC	Imaging	Comments
						Type	Injection site	Volume	Type	Injection site	Dose (in MBq)									
Feranec *et al.*	2010	21	17	1	1	PB	SE	N/A	NC	SE	100	61	G1 13; G2 3; G3 5	IA 4; IB 10; IIA3; IIB2; IIIA 1; IIIC 1	Common iliac 6; external iliac 2; Internal iliac 2; Interiliac 7; Obturator 4; para-aortic upper 6; lower7	N/A	LP	0	Planar 60 min post-injection/In some cases SPECT/CT was used	All sentinel nodes were hot / no blue cold node was detected/only in 15% blue dye was successful
Dittmann *et al.*	2010	62	48	2	2	N/A	N/A	N/A	NC	SE	300-350	N/A	N/A	N/A	N/A	N/A	LP	N/A	SPECT/CT 3-5 h post-injection	Most of the failures occurred during learning curve.
Sola *et al.*	2010	15	12	N/A	N/A	N/A	N/A	N/A	NC	SE	111 /8 ml two deposits	N/A	N/A	N/A	N/A	N/A	LPS	N/A	Planar 2 and 4 h and SPECT/CT 4 h post injection	Portable gamma camera showed 10/15 and imaging 12/15 nodes
Mais *et al.*	2010	17	14	2	2	PB	C	4 ml/in 4 deposits	N/A	N/A	N/A	61	G1 11; G2 4; G3 2	Ib 14; Ic 1; IIIa 2	Pelvic region mostly internal iliac	N/A	LPS	N/A	N/A	The authors considered failure to detect SLNs in the patients with lymph node involvement as false negative: The false negative cases were recalculated from the original study
Mais *et al.*	2010	17	7	1	1	PB	C	4 ml/in 4 deposits	N/A	N/A	N/A	65.9	G1 6; G2 7; G3 4	Ia 1; Ic 1; IIIa 2	Pelvic region mostly internal iliac	N/A	LP	N/A	N/A	The authors considered failure to detect SLNs in the patients with lymph node involvement as false negative: The false negative cases were recalculated from the original study
Ballester *et al.*	2011	125	111	19	16	PB	C	2 ml/in 2 aliquots	USC	C	80 /in 4 aliquots (0.2 ml each)	63	G1,2 90 G3 10	IA 31; IB 45; IC; IIA 6; IIB 1	All pelvic except 5 patients	77	LPS 83 LP 82	9	Planar 2 h post injection and then every 30 minutes	Detection rate: 86/96 LPS and 25/29 LP-failure in 14 in whom 1 had metastasis
Cordero Garcia *et al.*	2012	19	17	0	0	MB	C	2 ml/in 2 aliquots	NC	C	74 /2 doses	39-84	G1 12; G2 6; G3 1	IA 7; IB 10; II 1; IIIA 1	Pelvic in 15 and both pelvic and extrapelvic in 2	3	LP	N/A	Planar and SPECT/CT 30 min post-injection and 16 hours imaging in case of non-visualization	Detection rate by lymphoscintigraphy was 16/19

following table 2. — *Summary of the included studies information.*

First author	Year	No. of patients	No. of patients with detected SN	No. of patients with posit. pelvic	No. of patients with positive SN	Blue dye			Radiotracer			Mean age	Grade	Stage	SLN distribution	No. of patients with bilateral drainage	Type of surgery	No. of positive node using IHC	Imaging	Comments
						Type	Injection site	Volume	Type	Injection site	Dose (in MBq)									
Barlin *et al.*	2012	425	339	37	32	IB or MB	C (in 34 also SS)	4 ml (2 ml deep, 2 ml superficial)	N/A	N/A	N/A	61	Predominantly GI (392 patients)	I, 392; II, 12; III, 85; IV, 9.	Pelvis in 384, peri-aortic region in 2 (not known if they are in the group with fundal injection or not), and in both the pelvic and peri-aortic area in 15 (not known if they are in the group with fundal injection or not)	253/401	LPS 147; RA 189; LP 89	9 out of 32	N/A	The information was extracted after subtraction of the data from Gemignani *et al.* study.
Leitao *et al.*	2011	119	88	N/A	N/A	IB or MB	C	4 ml (2 ml deep, 2 ml superficial)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	RA	N/A	N/A	The RA group
Leitao *et al.*	2011	151	136	N/A	N/A	IB or MB	C (in 22 also SS)	4 ml (2 ml deep, 2 ml superficial)	FSC (in 47)	C	37-148 / 0.5-1 ml	N/A	N/A	N/A	N/A	N/A	LPS	N/A	N/A	The LPS group
Rossi *et al.*	2012	16	14	2	1	ICG	C	1 ml in two aliquots	N/A	N/A	N/A	61	G1 9; G2 2; Other histologies 5	N/A	N/A	N/A	RA	N/A	Imaging was performed intraoperatively using near infrared	
Holloway *et al.*	2012	35	35	10	9	IB and ICG	C	1-2 ml IB and 0.5 ml ICG in four aliquots	N/A	N/A	N/A	63.4	G1 13; G2 14; G3 8	N/A	2 pre-sacral and lower aortic; 3 common iliac; the remainder in the pelvis	All patients using both methods 34 patients using ICG only	RA	4 out of 10	Imaging was performed intra-operatively using near infra red	Detection rate for both methods were 100%. However bilateral detection rate was 34/35 for ICG and 27/35 for IB method
Buda *et al.*	2012	25	22	3	3	MB	C	1 ml in two aliquots	NC	C	4 injection of 5-7.5/ 0.2-0.3	N/A	N/A	I	No para-aortic sentinel nodes	N/A	LPS or LP	2 out of 3	Both planar and SPECT/CT imaging 3 hours post-injection	Most of the information in the article was from a combination of cervical and endometrial cancer patients
How *et al.*	2012	100	92	9	8	PB	C	0.9 ml / 4 injections	FSC	C	0.1 ml/ dose is not available	63	GI 51; GII 20; GIII 29	I 86; II 1; III 13	Pelvic only 77 patients; para-aortic only 3 patients; both locations 12 patients	66 out of 92	RA		N/A	No learning curve effect was reported
Solima *et al.*	2012	76	80	10	9	N/A	N/A	N/A	NC	SE	111/ 5 ml	57.7	GI 4; GII 37, GIII 18	I 39; II 5; III 14; IV 1	Pelvic only 26; para-aortic only 2; both locations 31	N/A	LP 49; LPS 10	6 out	Dynamic for of 10 and static views every 5 minutes for 1 hour	– 15 minutes

IB: isosulphane blue, PB: patent blue V, MB: methylene blue, SS: subserosal, SE: subendometrial, C: cervical, NC; nanocolloid, FSC: filtered sulfur colloid, USC: unfiltered sulfur colloid, P: phytate, HAS: human serum albumin, RSC: rhenium sulfide colloid, LP: laparotomy, LPS: laparoscopy, RA: robotic-assisted laparoscopy.

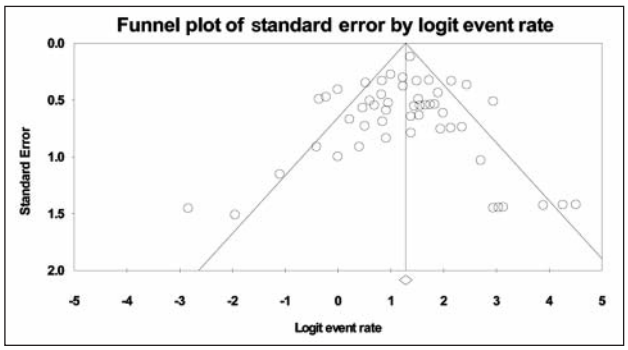

Figure 3. — Funnel plot of the detection pooling rate.

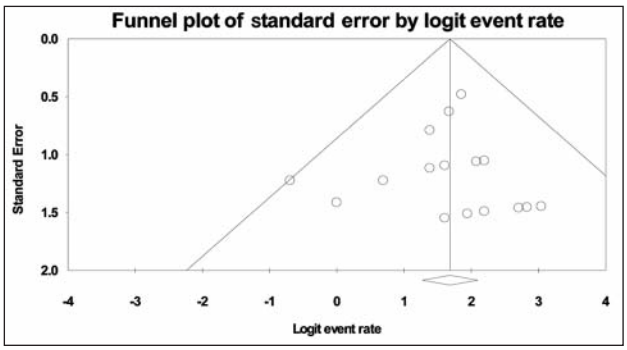

Figure 5. — Funnel plot of the pooling sensitivity.

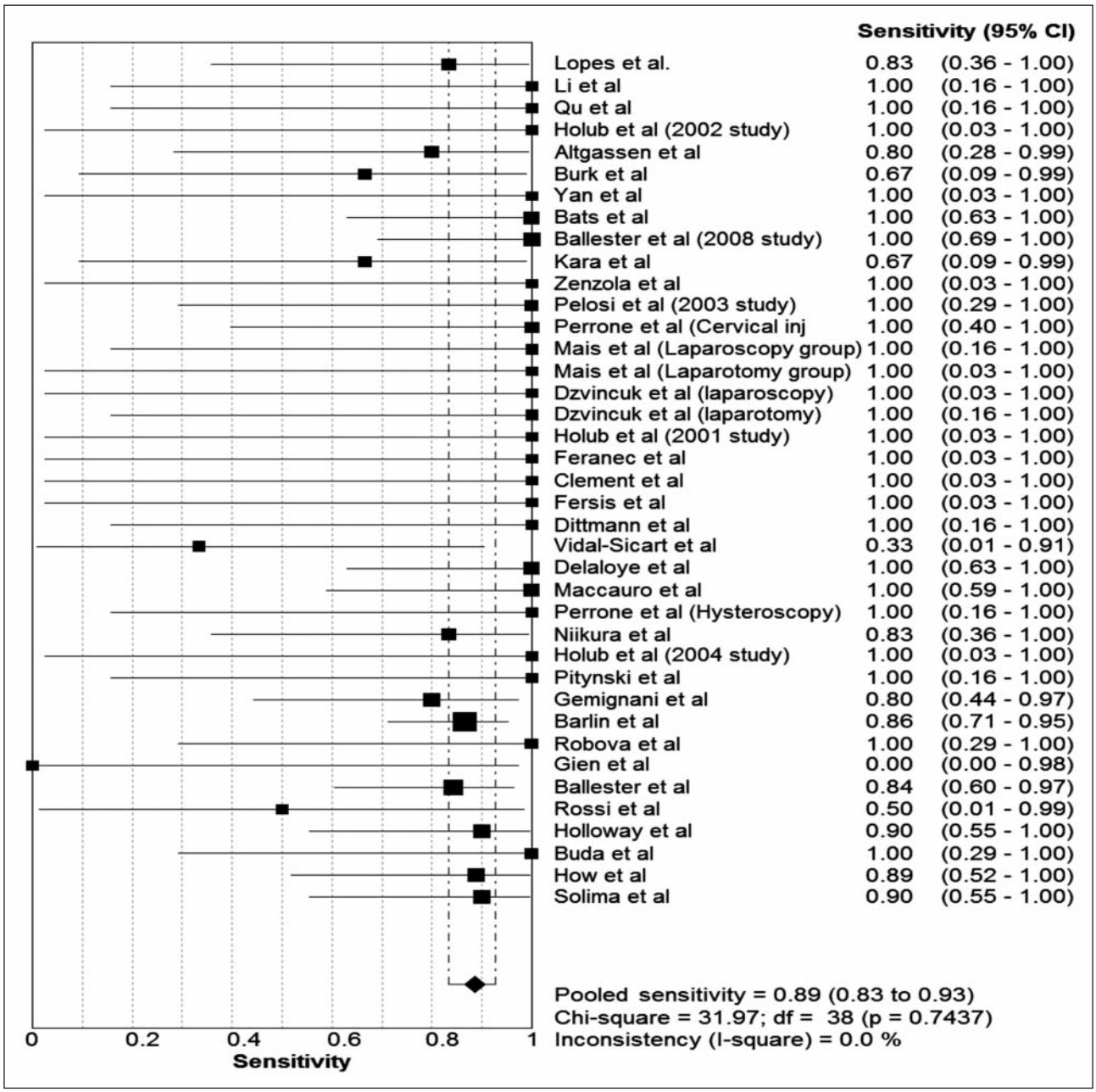

Figure 4. — Forrest plot of the pooling sensitivity.

Learning curve effect

Introduction of sentinel node mapping into a surgical community needs certain time for the surgeons to gain enough experience. This concept has been shown in breast cancer surgery [60]. In the present meta-analysis, several studies reported learning curve effect on the mapping success. Khoury-Collado *et al.* reported that four out of five false negative cases in their study occurred when surgeons had less than ten patients experience, and detection rate during 2006 and 2007 was 37/46 while during 2008-2010 it was 82/86 [7]. Zenzola *et al.* reported that four detection failure in their study was in their first patients [44]. Delaloye *et al.* also reported that all 11 failures occurred during learning curve phase [31]. Dittmann *et al.* reported that most of the failures occurred during learning curve without giving any information [48]. Finally Li *et al.* reported that their first four patients had defective injection which were excluded from the analysis [40].

Overall, it seems that learning curve effect is also present in sentinel node mapping of endometrial cancer (high false negative and low detection rate) and surgeons should consider it before routine use.

Publication bias

Publication bias is an important issue which should be addressed in all systematic reviews. For minimizing this bias, the present authors searched several databases and exerted no language limit in this search. They also included meeting abstracts to the systematic review. One study in Polish [20], two studies in Czech [26, 47], three studies in Chinese [29, 35, 46], and two studies in Spanish [44, 55] were included. Six of the included studies were meeting abstracts [27, 33, 45, 48, 49, 52], one was a proceeding paper [19], and one was a thesis [35].

Despite these efforts, funnel plots of detection rate and sensitivity pooling showed some asymmetry, although Egger's test was not statistically significant in either one. This shows that publication bias can be a concern in the present meta-analysis as an important limitation.

Limitations

One of the major limitations of th present study is the quality of the included studies. Twenty-nine of the included studies did not recruit patients in a consecutive fashion. The spectrum of the included patients was not broad enough in some groups. For example Gien *et al.*, Burke *et al.*, and Frumovitz *et al.* only included patients with high risk of metastasis in their study [15, 25, 32]. Most importantly, the gold standard used by most studies was pelvic lymphadenectomy and para-aortic lymph node dissection that was performed in selected cases or not performed at all. Only ten studies included routine para-aortic lymphadenectomy in their study [15, 16, 24, 28, 31, 32, 41, 43, 46, 54]. This can influence the false negative rate of the present meta-analysis and is a major limitation this our study.

Another limitation is the low incidence of positive lymph nodes in endometrial carcinoma. Many studies included in this meta-analysis only had one patient with positive lymph nodes and overall 187 patients with positive nodes were included in the current systematic review. Although limiting the sensitivity pooling to the larger series did not affect the sensitivity (89% sensitivity when including only studies with more than five patients with involved nodes), it seems that larger studies with more positive lymph node patients are still required before considering sentinel node mapping a safe method in endometrial cancer.

Conclusion

Sentinel node mapping is feasible in endometrial cancer. Cervical injection, as well as using both blue dye and radiotracer, results in the highest detection rate and sensitivity. Larger studies are still needed to evaluate the false negative rate and the factors influencing the sensitivity in more detail.

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Address reprint requests to:
R. SADEGHI, M.D.
Nuclear Medicine Research Center,
Imam Reza Hospital,
Ebn Sina St. Mashhad (Iran)
E-mail: sadeghir@mums.ac.ir
raminsadeghi1355@yahoo.com