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Research Article

A Review of Sentinel Node in Endometrial Cancer

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Introduction

Endometrial cancer (EC) is the most frequent gynecological cancer in the developed countries [1]. In Denmark, more than 800 new cases were diagnosed from July 2014 to July 2015 [2]. Standard treatment for FIGO stadium I-II is total abdominal hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection for the purpose of planning adjuvant chemotherapy. Pelvic lymphadenectomy (PL) is recommended for all patients with FIGO stadium IIB. Occasionally, it is recommended that para aortic lymph nodes be removed as well [3]. The treatment is based on a pre- and intraoperative assessment. Currently, MRI is recommended as part of preoperative staging by FIGO [2] to assist evaluating the myometrial invasion. Though, a study found a poor correlation between preoperative MRI-staging compared with biopsy-based stage [4] with only 12 of 46 women correctly staged by MRI [4].

Recently, two large randomized trials [5,6] have been published suggesting that PL has no impact on overall and disease-free survival rates in patients with early stage EC while exposing patients to the risk of complications. These trials didn't, however, take SLN mapping into account. Other studies seem to indicate that sentinel node biopsy is the most effective way to stage all patients with early stage endometrial cancer, instead of doing systematic PL [7,8].

Lymph node involvement appears in 6-12.5% of women with presumed low risk EC [9]. As a consequence, more than 70% of women undergoing lymphadenectomy do not benefit from the procedure and are over treated. Several peri-and postoperative complications are related to lymphadenectomy including lymphedema, lymphocyst formation, neurological complications and blood loss [10-13]. One third of women are diagnosed with lower limb lymphedema after the operation, which is associated with decreased quality of life affecting both pschological well-being and physical function [14].

A sentinel lymph node (SLN) is defined as the first lymph node to which the primary tumor may metastasize. However, many lymph nodes may have direct connection to the primary tumor, which is why it is important to recognize the possibility that several SLNs may exist [15].

SLN mapping may have several advantages compared to radical PL since only a few lymph nodes are removed. The intra- and postoperative complications decrease, shorter operation time and potentially leading to identification of occult metastatic disease in the form of SLN in areas e.g. paraaortal which would have been left with standard PL [15,16].

An additional advantage of the technique is the improved detection of micrometastasis through pathological ultrastaging [17]. Ultrastaging is a pathologic assessment of the SLNs and usually performed in addition to hematoxyline and eosin (H&E) staining. The principle is based on immohistochemistry where the expression of primarily cytokeratin is used as an expression for metastases [18].

Traditionally, a combination of blue dye and radioactive isotopes has shown the best detection rate for SLN mapping. Application of indocyanine green (ICG), a dye, which is flourescent in the near-infrared (NIR) spectrum, has gained increasing acceptance in lymphatic mapping [9]. The ICG technique improves the visualization compared to blue dye (BD) and disadvantages e.g. poor visualization is avoided [19].

SLN mapping is controversial and due to a lack of supporting evidence, it is not yet

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used in the daily treatment of women diagnosed with endometrial cancer.

SLN mapping has been proven safe in breast and melanoma cancer [20,21] while appearing promising in cervical and vulval cancer [22,23].

The objective of this review is to evaluate current data about the use of sentinel lymph node procedure in patients with endometrial cancer.

Materials and Methods

Articles were found by a comprehensive search in two electronic databases. Only English and Danish languaged articles were included. The search was applied to PubMed (2006-Present) and Embase (2006-Present). The following index terms were used in the electronic databases: "endometrial cancer" and "sentinel node." The search strategy allowed variation across the databases; in Pubmed these index terms were converted to "endometrial neoplasms" AND "sentinel lymph node biopsy" as Mesh terms while Embase converted the index terms to "endometrium cancer" AND " sentinel lymph node biopsi" as emtree terms. In terms of limits, articles where full text was not available were excluded whereas editorials, letter to the editors, conference meetings and clinical commentary were included. Articles published in journals with lower ranking [24] were excluded while impact factor was used to evaluate the article's relevance taken time of publication into consideration. To eliminate double counting, articles using the same cohorte in multiple publications were excluded.

Lymph node metastases were classified according to their size based on the definitions for nodal metastases in breast cancer [25]; isolated tumor cells (ITC) are <0.2mm, micrometastases are 0.2-2mm and macrometastases larger than 2mm.

From the 16 studies, results were extracted and recalculated to comply with the following standard definitions [26]:

- Detection rate: number of patients with at least one SLN identified divided by total number of patients who underwent procedure.
- Sensivity: number of patients with positive-SLNs divided by all patients with lymph node metastases. (true positive tests/all positive patients)
- True positive SLN: positive SLN identified with or without ultrastaging independent of the status of non-SLNs.

Of the included articles for this review, data used for analysing did not include metaanalyses and reviews.

In order to minimize learning curve bias, detection rates for each study were calculated based on all patients who underwent the procedure according to the above mentioned standard definitions rather than successfully mapped patients, explaining why some results in this review vary from results reported in the included articles.

Detection rate and sensivity were the two primary endpoints of this review. The tested variables included numbers of included patients, patients with at least one SLN detected, patients with no SLN detected, bilateral detection, patients with positive SLNs and patients with lymph node metastases.

The sensivity and detection rate were calculated in Excel individually and pooled for each study with available data according to the above described definitions. An approximately normal distribution was estimated to calculate exact 95% confidence interval (95%CI). No further adjustments were applied for statistical analysis. In order to compare this review's results with an included meta-analysis [27], detection rate, bilateral detection rate and sensivity were calculated for the meta-analysis following the same method as this review.

Results

Initially, the search identified a total of 223 articles; 99 and 124 articles from Pubmed and Embase, respectively. After adjusting for duplicates 178 articles remained. Of these, 100 were excluded based on a preliminary screening of title and abstract. According to eligibility criteria, studies with less than 35 patients were discarded. One additional study was discarded because full text of the article was not available. Based on journal ranking[27] and impact factor another 29 articles were discarded. 22 articles were screened by reading full text which excluded 9 articles; 2 due to identical cohorte as already included and 7 due to lacking relevance. The 5 most recent published articles' reference lists were examined and in this way, an additional 3 articles were handpicked and included based on the above mentioned eligibility criteria. Finally, 16 articles were included for this review [4,26,28-39]. Figure 1 summarizes the study selection.

This review included 16 studies of these 13 studies' data were analysed with a total of 1778 patients, their characteristics are summarized in Table 1.

By applying data from the 13 studies, calculations estimated a pooled detection and bilateral detection rate of 90,5% 95%CI[87,9;93,1] and 67,5% 95%CI[61,5;75,5], respectively and a pooled sensitivity of 87,5% 95%CI[83,9;91,0].

95%CI were defined from SE (SD) calculated as 1,30 and 3,08, for detection and bilateral detection. Detection rate were available for all 13 studies while bilateral detection rate only were available for 11 studies including 1358 patients.

The sensivity were based on 8 studies including 1248 patients. 95%CI was calculated from a SE (SD) = 1, 8.

Detection and bilateral detection rates of SLNs and sensivity are summarized in Tables 2 and 3.

The results were not assessed for inconsistency providing a risk of bias. The standard deviations express the heterogeneity across studies.

When comparing the contribution of ultrastaging to detected metastases in SLN the results vary from 25% to 67% in the 7 studies which provided obtainable data, as shown in Table 4. This makes a pooled contribution of 40%, in other words 40% of the 131 women with metastases were detected only by ultrastaging.

.Four studies including 433 patients compared colometric and flouremetric tracer modalitites where ICG showed a significantly higher bilateral detection rate than BD (Table 5).

For the purpose of allowing comparison of results, data from the included meta-analysis [26] were used to estimate none adjusted values [1] defining a detection rate, bilateral detection and sensivity

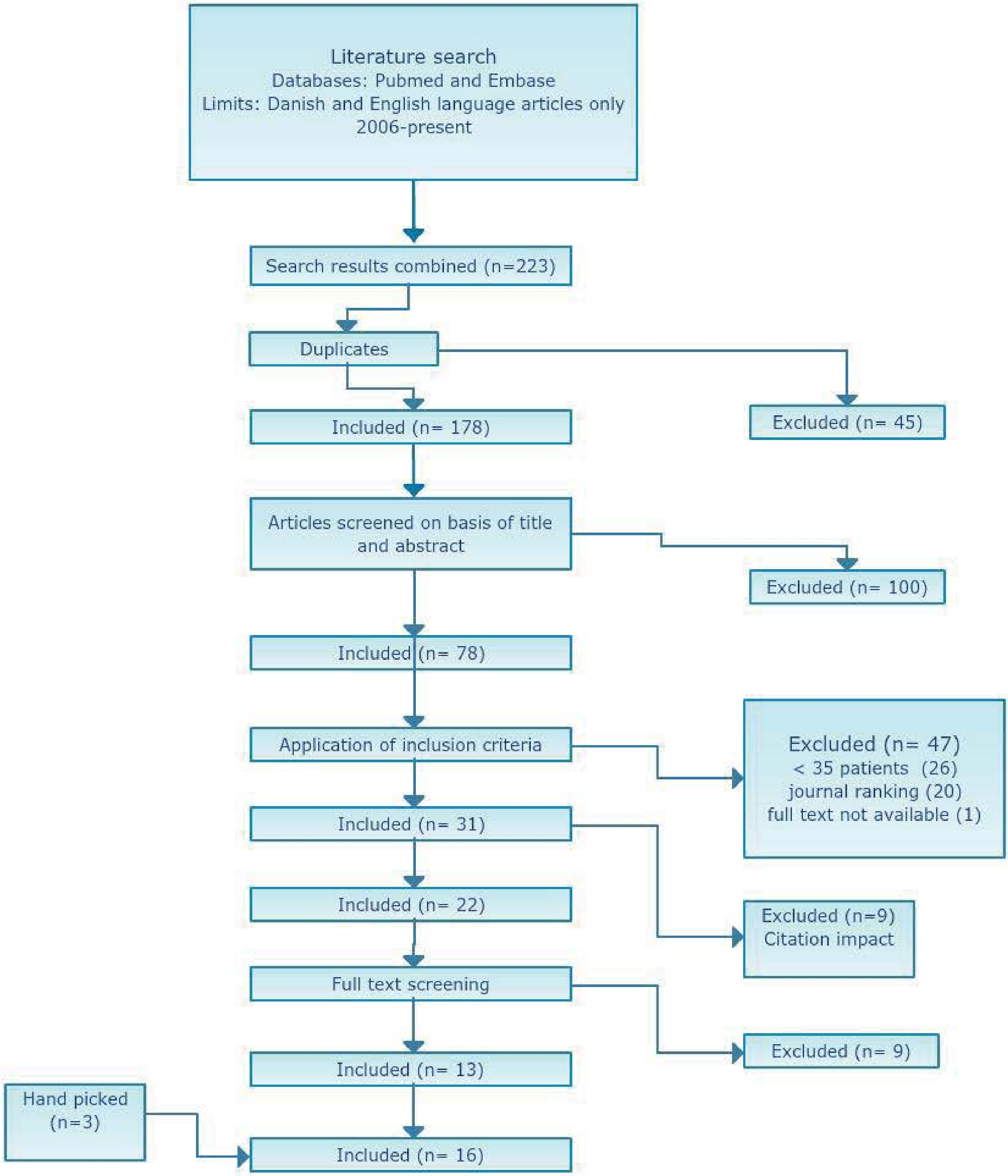

Figure 1: Study selection.

as 76,0% [71,2;80,9], 53% [45,1;60,9] and 89,2% [82,6;95,8], respectively following the algorithm used in Tables 2 and 3.

The SE (SD) used for the detection rate were 2, 5 with data from 26 studies, the SE(SD) for the bilateral detection rate were 4,0 based on 14 studies and the SE(SD) for the sensivity was 3,4 based on 21 studies.

Author	Year	N	Injection method	Injection site	Tracer	Detection method	Route of surgery	Pathology assessment	Study type
Abu-Rustum	2009	42	Intracervical	Cervix/Fundus	BD/TC	Both	laparoscopy/laparotomy	HE/IHC	Prospective
Ballester, Ballester	2011	125	Intracervical	Cervix	BD/TC	Both	laparoscopy/open surgery	HE/IHC	Prospective
Dubernard	2008	46	Intracervical	Cervix/Fundus	BD/TC	Both	laparoscopy/laparotomy robotic	HE/IHC	N/A
Barlin	2012	498	Intracervical	Cervix	BD/TC	Dye	laparoscopy/laparotomy	HE/IHC	N/A
Holloway	2012	35	Intracervical	Cervix	ICG/BD	Both	robotic	HE/IHC	N/A
How, Gotlieb	2015	100	Intracervical	Cervix	ICG/BD/TC	Both	robotic	HE/IHC	N/A
How, Lau	2012	100	Intracervical	Cervix	BD/TC	Both	robotic	HE/IHC	Prospective
Jewell	2014	227	Intracervical	Cervix	BD/TC	Both	robotic	N/A	Retrospective
Papadia	2016	75	Intracervical	Cervix	ICG	Isotope	laparoscopy	HE/IHC	N/A
Sinno	2014	81	Intracervical	Cervix	BD/ICG	Both	robotic	N/A	N/A
Solima	2012	80	Intracervical	Cervix	TC	Isotope	laparoscopy/laparotomy	HE/IHC	Prospective
Tanner	2015	111	Intracervical	Cervix	ICG/BD	Both	robotic	HE	N/A
Touhami	2015	268	Intracervical	Cervix	BD/TCb	Both	robotic/laparoscopy/laparotomy	HE/IHC	N/A

N/A = not available, BD = Blue dye, TC = Technetium-99 microsulfur, ICG = Indocyanine green, HE =Hematoxylin and eosin staining, IHC = immunohistochemistry.
[a]Used unfiltered technium sulphur colloid
[b]Used antimony trisulfid colloid (ATC) technetium-99

Table 1: Characteristics of 13 studies used for analysis.

Author	*N*	*Min one SLN detected*	*None SLN detected*	*Overall detection % (SD)*	*Bilateral detection*	*Bilateral detection % (SD)[a]*
Abu-Rustum	42	36	6	85,7 (4,8)	N/A	N/A
Ballester	125	111	14	88,8 (1,7)	77	61,6 (5,9)
Ballester, Dubernard	46	40	6	87,9 (3,5)	25	54,3 (13,2)
Barlin	498	401	24	80,5 (10,0)	253	50,8 (16,7)
Holloway	35	35	25	100 (9,5)	27	77,1 (9,6)
How, Gotlieb	100	92	8	92,0 (1,5)	76	76,0 (8,5)
How, Lau	100	92	8	92,0 (1,5)	66	66,0 (1,5)
Jewell	227	216	11	95,2 (4,7)	179	78,9 (11,4)
Papadia	75	72	3	96,0 (5,5)	66	88,0 (20,5)
Sinno	81	69	12	85,2 (5,3)	44	54,3 (13,2)
Solima	80	76	3	95,0 (4,5)	N/A	N/A
Tanner	111	95	16	85,6 (4,9)	69	62,2 (5,3)
Touhami	268	252	16	94,0 (3,5)	197	73,5 (6,0)

[a]Data only available for 8 studies.
SD = standard deviation

Table 2: Detection and bilateral detection rate.

Author	*N*	*True pos SLN*	*Lymph node metastases*	*Sensitivity %(SD)[a]*
Abu-Rustum	42	4	4	100 (12,53)
Ballester	125	16	19	84,2 (3,26)
Barlin	498	40	47	85,1 (2,36)
Holloway	35	9	10	90 (2,53)
How, Gotlieb	100	9	10	90 (2,53)
How, Lau	100	8	11	72,7 (14,74)
Solima	80	9	10	90 (2,53)
Touhami	268	43	49	87,8 (0,29)

[a]Data only available for 8 studies.
SD = standard deviation

Table 3: Sensivity

Table 6 summarizes provided data from the study along with calculated standard deviations.

The detection rate and bilateral detection rate were defined as 90,5% and 67,5% from this review and Kang et al, respectively suggesting a statistically significant difference as the confidence intervalls do not intersect. The deviating 95% confidence intervalls and standard deviations indicate between study heterogeneity. The sensivity however, seems reliable with this review estimated to 87,5% compared with 89,2% from Kang, et

Author	*N*	*True pos SLN*	*SLN deteced on ultraging*	*MaM*	*MiM*	*Isolated tumor cells*	*Proportion of metastatic patients detected only by ultrastaging (%)[a]*
Abu-Rustum	42	4	1	N/A	N/A	N/A	1/4 (25)
Ballester, Ballester,	125	16	9	8	7	1	9/16 (56)
Dubernard	46	10	4	3	7	0	4/10 (40)
Barli	498	40	9	N/A	N/A	N/A	9/40 (23)
Holloway	35	9	4	N/A	N/A	N/A	4/9 (44)
Solima	80	9	6	3	3	3	6/9 (67)
Touhami	268	43	19	24	7	12	19/43 (44)

[a]Data only available for 7 studies.
MaM =macrometastases
MiM = micrometastases

Table 4: Contribution of Ultrastaging.

Author	**Year**	**N**	**ICG (N)**	**BD (N)**	**Bilateral detection rate with ICG (%)**	**Bilateral detection rate with BD (%)**
Jewell	2014	227	197	30[a]	156/197 (79)	23/30 (77)
Holloway	2012	35	35	35	34/35 (97)	27/35 (77)
How, Gotlieb	2015	100[b]	100	100	65/100 (65)[c]	43/100 (43)[d]
Sinno	2014	71	38	33	30/38 (79)	14/33 (42)

[a]recieved both BD and ICG, but BD used as tracer.
[b]recieved ICG, BD and Technetium-99 microsulfur (TC)
[c]detection rate for ICG and TC
[d]detection rate for BD and TC

Tabel 5. Detection rate for ICG versus BD.

Author	*Detection rate %[a](SD)*	*Bilateral detection rate %[a] (SD)*	*Sensivity %[a] (SD)*
Burke	67 (9,0)	N/A	50 (39,2)
Gargiulo	100 (24,0)	55 (2,0)	100 (10,8)
Peolosi	94 (18,0)	56 (3,0)	100 (10,8)
Pitynski	88 (12,0)	N/A	N/A
Fersis	70 (6,0)	20 (33,0)	100 (10,8)
Houlb	84 (8,0)	81 (28,0)	100 (10,8)
Lelievre	92 (13,0)	27 (26,0)	100 (10,8)
Niikura	82 (6,0)	N/A	100 (10,8)
Gieb	44 (32,0)	N/A	0 (89,2)
Macccauro	100 (24,0)	N/A	100 (10,8)
Dzvincuk	79 (3,0)	N/A	N/A
Altgassen	91 (15,0)	N/A	67 (22,2)
Dealoye	50 (26,0)	45 (8,0)	89 (0,2)
Frumovitz	45 (31,0)	39 (14,0)	N/A
Li	75 (1,0)	73 (20,0)	100 (10,8)
Lopes	78 (2,0)	N/A	83 (6,2)
Ballester	87 (11,0)	63 (10,0)	100 (10,8)
Bats	70 (6,0)	53 (0)	100 (10,8)
Perrone	65 (11,0)	27 (26,0)	100 (10,8)
Robova	67 (9,0)	67 (14,0)	100 (10,8)
Vidal-Sicart	62 (14,0)	N/A	N/A
Zenzola	71 (5,0)	N/A	100 (10,8)
Feranec	81 (5,0)	N/A	100 (10,8)
Mais	62 (14,0)	N/A	100 (10,8)
Ballester	89 (13,0)	69 (16,0)	84 (5,2)
Khoury-Collado	84 (8,0)	67 (14,0)	N/A

[a]From Table 2 Kang et al.
SD = standard deviation

Table 6: Pooled detection rate, bilateral detection rate and sensivity from Kang, etal. not adjusted for heterogeneity.

al. confirming a value within the expected range hence, making the results not statistically significant which the confidence intervalls show.

Pooled detection rate, bilateral detection rate and sensivity from Kang, et al. [26] not adjusted for heterogeneity [2].

Discussion

This review found a detection rate and sensivity of 90,5% and 87,5%, respectively for SLN mapping in women with EC. The detection rate is an important measure because successful mapping may determine the clinical usefulness and represent a measure for the procedure's diagnostic accuracy [26].

Our results seem consistent with other studies evaluating SLN mapping in EC with a detection rate varying from 80-100% [28,40]. However, our results are higher compared with SLN mapping in vulval and cervical cancer with recovered detection rates of 84% and 89% [41], respectively while lower than a recovered detection rate for breast cancer of 96% [42].

Only one of the 13 studies included used hysteroscopic injection of the tracer with a detection rate of 95%. The remaining 12 studies injected the tracer into the cervix with detection rates from 85% to 100%. Injection method has been discussed varying between hysteroscopic, fundal and intracervical methods in attempt to identify uterus' drainage most clearly which also includes common iliac and paraaortic areas in addition to parametrial involvement as seen in cervical cancer [4]. Perrone, et al. [43] indicated that hysteroscopic injection provides complete visualization of lymphatic drainage as presented by the paraaortic lymph nodes. The most common method however, is cervical injection because it provides a high detection rate with minimal risk of missing aortic SLNs compared with inducing other injection sites and sparing the patients additional anesthesia. Furthermore it is suggested as the easiest and most reproductible method for SLN mapping [32]. In the included meta-analysis [26], cervical injection was significantly associated with an increased detection rate compared with hysteroscopic injection. In comparison, a recent review found high detection rates for cervical (62-100%) and corporal injections (73-95%) as well as suggesting the sampling size's relevance for the outcome, which will be discussed further below.

Also in terms of the tracer modality, several possibilities have been suggested considering benefits and disadvantages. As mentioned in the introduction, the combination of blue dye and radioactive isotopes has commonly been preferred with a high detection rate of 86% [44].

Technetium 99 is the preferred radioactive isotope because of its short half-life which allows rapid detection with low radiation exposures. It can be traced using a gamma probe either by hand or laparoscopically however, difficulties in detecting parametrial SLNs and distinguishing actual SLNs from the injection site uptake are reported consistently. Furthermore, clinical practice has been a challenge for obese patients where visceral fat has challenged detection when using the handheld probe [36]. Detection rate using technetium alone has been reported to 82% [45].

Visible dyes in the form of blue dyes are due to their biochemical structure and lower expense useful if injected intraoperatively to save the patient further anesthesia. Different kinds of colorimetric dyes are described, in this review they are referred to as blue dye (BD) collectively. Detection rate ranges from 75-92% and allergic reactions have been reported.

Flourescence imaging using ICG detected with the use of NIR has as mentioned in the introduction, already showed impressive detection rates. A disadvantage of the use with ICG and NIR however, is the expensive and advanced equipment required. This technique is applicable with laparotomy, laparoscopy and robotic-assisted surgery - the latter, finding increasingly favored amongst surgeons in terms of work postures during an operation. Several studies in this review compared ICG with BD and found a significant higher bilateral detection rate for ICG from 79-97% compared with BD 42-77% [35,36]. Two studies recommend a combination of ICG and BD to increase the bilateral detection rate [31] while another study concluded that BD may not be essential if a combination of BD and TC are used [34].

The use of ICG as a tracer seems favorable compared with BD due to increased technical visuality in particularly obese women who represent a large proportion of the EC patients [36]. Tanner, et al. [38] found BMI> 30 as point of intersection from where the rate of successful bilateral mapping decreased.

The uterus is a midline structure therefore, it is important to evaluate bilateral detection to avoid unilateral lymph node dissections. The 13 studies used for analysis differ in bilateral detection rate from 50% to almost 90% making a pooled bilateral detection rate of 67,5%.

For successful SLN mapping, two key principles have been recommended. Barlin, et al. [30] suggested that applying an algorithm to determine the false-negative rate goes beyond the removal of SLNs. In other words, excision should include both SLNs as well as clinically suspicious nodes along with side-specific retroperitoneal lymphendenectomy and ultrastaging to detect metastases. The algorithm is shown in Figure 2. The additional contribution in detecting metastases particularly, micrometastases through ultrastaging is established in this review with as many as 40% of the metastases in the 13 included studies which would have been missed without ultrastaging [3]. A recent study showed the risk of detecting NON-SLN metastasies in patients with positive SLNs and concluded a 35% possibility. The only predictive factor was the size of the SLN metastasis. They suggested a SLN algorithm where pelvic and paraarotic

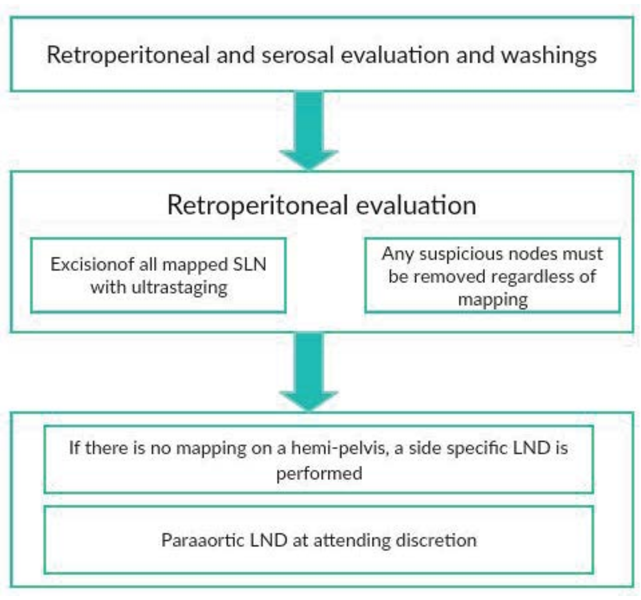

Figure 2: Surgical algorithm for EC.

lymphadenenctomy should be based on frozen section rather than ultrastaging [39].

The value of detecting micrometastases seems much debated however, Ballester, et al. [4] argue that ultrastaging in some cases will upstage women and thereby qualify them for adjuvant treatment and significantly increases disease-free survival. Meanwhile Raimond, et al. [46] failed to find an impact on recurrence free survival when using SLN biopsies to tailor adjuvant therapy to women with micrometastases compared to women with negative SLNs. Latest research suggests that the prognostic value of micrometastases still seems uncertain, it is important not to increase use of adjuvant therapy based hereof.

The other considerable recommendation with regard to successful clinical SLN mapping comes from Khoury-Collado, et al. [47] who emphasizes the association between the surgeon's learning curve and successful SLN mapping. According to their study, an improved detection rate from 77-94% was registered after 30 SLN procedures. Having this in mind, this also applies for histopathologists (Figure 2).

Research in this area currently seems inadequate in order to finalize SLN mapping's role in women diagnosed with early-stage EC. The advantages include significantly lowering blood loss and reducing surgery time compared with lymphadenectomy, which suggest a therapeutic and diagnostic benefit.

Despite the investigation of tracer modality, injection method and method of surgery; few studies seem to combine the same methods with a significant sampling size making comparison challenging. Therefore, when comparing cumulative results across studies with different methods potential bias should be considered this is the main limitation of this review.

For future standization, Cormier, et al. [31] recommend using standard definitions and checklists allowing interpretation across studies. For additional improvement of the SLN technique, increased SLN detection rate with SPECT-CT prior to surgery has been suggested as this in one study increased the detection rate of SLN to 100% compared with planar lymphoscintigraphy [48].

This study has several limitations. Study effects including small study effects and heterogeneity between studies were not evaluated in the statistical calculation and therefore taken into consideration when assessing the results. In contrary, small study effect were to some degree accounted for as studies with less than 35 patients were not included. The heterogeneity could have been adjusted through the use of an I^a-test however, due to the probability of suggesting a homogeneity this was left out. Selective reporting bias may effect cumulative results, as some studies failed to report or measure the outcomes evaluated in this review.

In conclusion, the results of this review indicate that SLN mapping is a highly specialized treatment which can avoid lymphadenectomy in many cases without compromising the diagnostic safety**.** Furthermore, SLN mapping can help tailor adjuvant therapy while patients can avoid complications related to lymphadenectomy. Cervical injection is the most common injection method based on feasibility and high detection rates while ICG in combination with BD or TC is gaining increasingly progress. Although promising results are found, further research is necessary to confirm the clinical evidence before introducing the technique as part of EC treatment.

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