

Sentinel lymph node mapping in endometrial cancer: a literature review and state of the art

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ABSTRACT

Objective: Sentinel lymph node biopsy has proven safe and feasible in a number of gynecologic cancers such as vulvar cancer, cervical cancer, and endometrial cancer. The aim of sentinel node mapping is to decrease the morbidity associated with a complete lymphadenectomy, while also increasing the detection rate of small lymph node metastases. The scope of this review is to critically appraise the published literature on (Sentinel Lymph Node) SLN procedure in endometrial cancer (EC).

Methods: We run a PubMed search for publications in English using "endometrial cancer" and "sentinel node" as key words. All abstracts from 2005 to December 2015 were reviewed. We excluded studies aimed to determine the risk of metastasis in the remaining non-SLNs when the SLN is positive, studies that only reported on successfully mapped patients, those where different types of gynecological cancers other than EC and/or atypical endometrial hyperplasia were included and those studies with less than 30 cases.

Results: 23 studies met the inclusion criteria. The overall detection rate of sentinel nodes after cervical injection ranged from 62% to 100%, while it was 73% to 95% after corporeal injection. All studies with n of cases \geq 100 had overall detection rates of $>80\%$. In terms of product/tracer used, Technetium colloid, blue dye and ICG were used either alone or in combination. Detection rates were good for all three products, however, detection rates were higher when blue dye was combined with Technetium (Tc) or Indocyanine Green (ICG). The injection site influenced the pattern of sentinel mapping with para-aortic SLNs being found more often using corporeal and deeper (3–4 cm) cervical injection techniques. Studies in which the protocol included a systematic para-aortic lymphadenectomy had higher detection of para-aortic SLNs, as well as isolated para-aortic metastases.

Conclusion: Sentinel lymph node mapping for endometrial cancer balances the need to assess nodal disease with the low likelihood of nodal metastasis for most patients. It is a technique with minimal morbidity, sparing the need for a full lymphadenectomy and its associated higher morbidity potentially leading to a greater utilization by gynecologic surgeons in the future. Achieving high bilateral SLN detection rates and low false-negative rates is mandatory to implement the SLN mapping as a routine component of clinical practice.

Keywords: Sentinel Lymph Node Mapping, Endometrial Cancer, Indocyanine Green

SOMMARIO

Obiettivi: La biopsia del linfonodo sentinella si è dimostrata sicura e fattibile in vari tipi di tumori ginecologici, come nei tumori della vulva, della cervice e dell'endometrio. L'obiettivo della procedura del linfonodo sentinella nel tumore dell'endometrio è quello di diminuire la morbilità associata con una linfadenectomia totale ed allo stesso tempo incrementare l'individuazione di micrometastasi linfonodali. Lo scopo di questa review è di valutare criticamente la letteratura pubblicata sulla procedura del linfonodo sentinella nel tumore dell'endometrio.

Metodi: Abbiamo eseguito una ricerca su PubMed per pubblicazioni in lingua inglese utilizzando "endometrial cancer" e "sentinel node" come parole chiave. Sono stati rivisti tutti gli abstracts dal 2005 al Dicembre 2015. Abbiamo escluso gli studi il cui unico obiettivo era quello di determinare il rischio di metastasi nei rimanenti linfonodi "non-sentinella" quando il linfonodo sentinella risultava positivo, studi che riportavano solo pazienti in cui la procedura aveva avuto successo, quegli studi che includevano diversi tipi di tumori ginecologici oltre al cancro dell'endometrio e studi con un numero di casi inferiore a 30.

Risultati: 23 studi hanno risposto ai nostri criteri di inclusione. Il tasso d'identificazione complessivo dei linfonodi sentinella è risultato variare tra il 62% ed il 100% dopo iniezione cervicale e tra il 73% ed il 95% dopo iniezione nel corpo dell'utero. Tutti gli studi con un numero di casi \geq 100 hanno mostrato un tasso di identificazione complessivo maggiore dell'80%. Riguardo al tracciante/prodotto utilizzato, il Tecnezio99m (tc), i coloranti blu ed il verde di indocianina sono stati usati da soli o in combinazione. I tassi d'identificazione sono risultati buoni per tutti i prodotti utilizzati, ma si sono evidenziati risultati migliori quando il colorante blu è stato utilizzato in combinazione con il tecnezio o con il verde di indocianina. Il sito d'iniezione ha influenzato la localizzazione dei linfonodi sentinella individuati, mostrando che i linfonodi sentinella para-aortici vengono individuati più frequentemente quando sono utilizzate tecniche di iniezione nel corpo uterino o più profondamente nella cervice (3-4 cm). Gli studi in cui i protocolli prevedevano una linfadenectomia para-aortica sistematica hanno mostrato un tasso maggiore d'identificazione di linfonodi sentinella para-aortici così come un tasso maggiore di metastasi isolate dei linfonodi para-aortici.

Conclusioni: La procedura del linfonodo sentinella nel tumore dell'endometrio consente di bilanciare la necessità di valutare l'eventuale presenza di malattia linfonodale con la scarsa probabilità di metastasi linfonodali nella maggior parte delle pazienti. E' una tecnica gravata da una minima morbilità. Risparmiando la necessità di una linfadenectomia totale con i suoi maggiori rischi di morbilità e di mortalità rappresenta una tecnica che può potenzialmente divenire nel prossimo futuro di maggiore utilizzazione da parte dei chirurghi ginecologi. E' mandatorio ottenere un alto tasso d'identificazione bilaterale e bassi tassi di falsi-negativi al fine di poter includere la procedura del linfonodo sentinella come una metodica di routine nella pratica clinica.

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INTRODUCTION

Sentinel Lymph Node (SLN) mapping is currently gaining popularity in gynecology oncology. The advantage of a sentinel node biopsy is lower morbidity than full lymphadenectomy and the potential for improved diagnostic accuracy. SLN biopsy has revolutionized treatment of breast cancer and melanoma, and the accuracy results in early stage vulvar and cervical cancers have been very encouraging⁽¹⁻⁵⁾.

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, with more than 54,000 new cases estimated for the year 2015 in the United States⁽⁶⁾. Despite this high prevalence, management is an issue of significant debate and controversy. Balancing complete staging information for both prognostic and potential therapeutic benefits against potential perioperative morbidity and mortality has been the aim of numerous studies to estimate the relationship between clinical and pathologic characteristics in endometrial cancer. Surgery is the standard of treatment of EC. In particular, hysterectomy (with or without salpingo-oophorectomy) allows to remove primary tumor and to identify patients at high-risk of developing recurrences. However, no consensus on the execution of retroperitoneal staging still exists. The American College of Obstetricians and Gynecologists recommended the execution of lymphadenectomy. Therefore lymph node staging remains an important part in EC treatment⁽⁷⁾. Different retrospective studies evaluated the role of lymphadenectomy suggesting the prognostic and therapeutic role of retroperitoneal staging⁽⁸⁾. However, these results were not supported by the two randomized trials comparing hysterectomy plus lymphadenectomy versus hysterectomy alone in the management of early stage EC⁽⁹⁾. In fact, they suggested that lymphadenectomy increases morbidity without improving oncologic outcomes. Although their study designs have been largely criticized because of big biases, these trials provide an overview of the lack of consensus on EC management⁽⁹⁾. Most patients with endometrial cancer will present with early-stage disease. Although the rate of metastasis in these patients is low, offering excellent prognoses, the standard of treatment in many practices still includes a complete or selective pelvic and para-aortic lymphadenectomy for staging; accurate surgical staging being the most important prognostic factor. Many patients will undergo a comprehensive lymphadenectomy despite having disease confined to the uterus, resulting

in prolonged operating time, additional cost, and potential side effects, such as lower extremity lymphedema. However, recent studies show that a complete lymphadenectomy may have no therapeutic benefit in patients with early-stage endometrial cancer⁽¹⁰⁾. SLN mapping, which has been used in other cancer types, may be an acceptable compromise between a complete lymphadenectomy and no nodal evaluation in patients with EC. SLN mapping is based on the concept that lymph node metastasis is the result of an orderly process; that is, lymph drains in a specific pattern away from the tumor, and therefore, if the SLN, or first node, is negative for metastasis, then the nodes after the SLN should also be negative. This approach can help patients avoid the side effects associated with a complete lymphadenectomy, although disease must be thoroughly staged for accurate prognosis and determination of appropriate treatment approach.

The aim of our study is to critically review the published literature on SLN procedure in EC. We hope to offer help refining the methodology that should be used and applied to future studies.

MATERIALS AND METHODS

We run a PubMed search for publications in English using “endometrial cancer” and “sentinel node” as key words. All articles from January 2005 to December 2015 were reviewed. Full relevant articles were assessed. We excluded studies aimed to determine the risk of metastasis in the remaining non-SLNs when the SLN is positive and to identify the factors that can predict the risk of lymph node metastases. Additionally, studies that only reported on successfully mapped patients and those where different types of gynecological cancers other than EC and/or atypical endometrial hyperplasia were excluded. We included only studies with a minimum of 30 cases using the same injection approach. In case of multiple publications from the same research team, the most recent study was selected.

Descriptive statistics were used. We considered injection site and injection product/tracer. Outcome measures were:

- Detection rates (defined as proportion of patients with at least one SLN detected)
- Sensitivity: patients with positive-SLN divided by all metastatic patients (true positive tests/all positive patients);
- Specificity: patients with negative-SLN divided by all non-metastatic patients (true negative tests/all negative patients)

- Negative predictive value: negative-SLN patients who are non-metastatic divided by all patients without a positive-SLN (true negative tests/true negative + false negative tests);
- False negative rate: metastatic patients without a positive-SLN divided by all metastatic patients (false negative tests/false negative + true positive tests);
- Unilateral versus bilateral mapping;
- Para-aortic mapping and the impact of ultra-staging

RESULTS

We identified 108 abstracts. Review articles, commentaries, meta-analysis or other types of publications that did not meet our inclusion criteria were excluded. We identified 86 retrospective/prospective studies. From these, 24 studies were excluded because they had less than 30 patients, 19 because they included patients with atypical endometrial hyperplasia or other gynecologic cancers, and 10 because they did not report results on all patients that underwent SLN procedure. 10 studies were not considered as they were from the same research team using the same database. In this case we only considered the most recent study.

23 studies met our inclusion criteria (11-34).

Among these studies different injection techniques have been used. Studies differ by injection site and injection product. We identified three different sites of injection; in the cervix, in the myometrium (subserosal) and peritumoral by hysteroscopy or by transvaginal ultrasonography. Cervical injection could be deep or superficial submucosal. To simplify we separated these in two categories: cervix and corporeal injections.

Of the 23 studies reviewed, 13 used cervix as the only injection site, 8 used a corporeal method of injection, and 2 studies used both injection sites in the same patient^(20, 29) (**Table 1**). The total number of patients in the cervical injection category was higher than the total number in the corporeal injection category (1437 versus 490). The overall detection rate of sentinel nodes after cervical injection ranged from 62% to 100%, while it was 73% to 95% after corporeal injection. All studies with $n \geq 100$ had overall detection rates of $>80\%$.

Regarding the product/tracer used, we identified: Technetium colloid, blue dye and indocyanine green (ICG). These could have been used alone or in combination. The choice of injection product depends on both its ability to be detected in the sentinel nodes and on its

ease of use. The injection agents identified in our review included technetium colloid (Tc), blue dye (methylene blue or lymphazurin), and (ICG). Technetium colloid can be detected for a longer period of time and therefore is often injected pre-operatively. Surgeons can be guided to the mapped regions by a pre-operative lymphoscintigram or SPECTCT, however correlation between imaging done the day before surgery and the intra-operative findings is low^(20, 34). It may be more difficult to detect SLNs close to the cervix as the gamma-probe picks up high activity from the injection site. The resources and equipment required for Tc mapping are cumbersome, costly, and are not available to all surgeons.

Blue dye is a much cheaper product and is widely available in most hospitals. It also is more convenient to use because it is injected intra-operatively, however it may be more difficult to detect in obese patients⁽³⁵⁾. Allergic reactions are known to occur; but severe reactions are very rare (0.1%)⁽³⁶⁾. ICG is a new injection agent that relies on near-infrared imaging. This method is expensive because it requires the use of specialized equipment; however early reports on its use in cervical and endometrial cancer suggest very high SLN detection rates^(35, 37, 38). Table 1 summarizes detection rates according to injection technique. Overall detection rates were good for all three products. However, detection rates were higher when blue dye was combined with Tc or ICG.

Furthermore, as the lymphatic drainage in the pelvis is not unilateral, bilateral detection rates are the most clinically relevant. Seventeen studies reported on bilateral sentinel node detection rates. It ranged from 34 to 100% for cervical injection. There are two studies using just corporeal injection that reported on bilateral detection having a rate of 37 and 19%^(16, 27). There may be a tendency for higher bilateral detection with cervical injection, and combining blue dye to Tc or ICG resulted in a higher bilateral detection rates than blue dye alone (Table 1).

One of the most debated aspects of the EC staging is the extent of lymphadenectomy and whether it should be performed in pelvic only or in pelvic and para-aortic full dissection. It has also been criticized that SLN mapping would translate to a low para-aortic detection rate. It has been a convention that uterine lymphatics drain through the paracervical tissues, but lymphatic drainage also occurs through the infundibulo-pelvic ligament or via pre-sacral lymphatics directly to the aortic bifurcation^(17, 39, 40). It was observed that the injection site influenced the pattern of sentinel

Table 1
Sentinel Lymph node detection rates by injection method and tracer used.

Author (reference)	N	Tracer Used	Injection Site	Overall detection rate (%)	Bilateral detection rate (%)
Ballester (11)	125	Blue dye + technetium	Cervix	89	62
Bats (15)	43	Blue dye + technetium	Cervix	70	37
Niikura ^a (13)	55	Blue dye + technetium	Cervix	78	49
Naoura ^c (31)	180	Blue dye + technetium	Cervix	88	63
Robova (14)	67	Blue dye + technetium	Corpus	73	NA
Delaloye (16)	60	Blue dye + technetium	Corpus	82	37
Niikura ^a (13)	55	Blue dye + technetium	Corpus	78	49
How [*] (17)	100	Blue dye + technetium	Cervix (deep)	92	66
Lopez-de la Manzanara (18)	50	Blue dye + technetium	Cervix (deep)	92	34
Mucke ^b (19)	31	Blue dye + technetium	Cervix (deep)	90	52
Sawicki [*] (20)	70	Blue dye + technetium	Cervix + Corpus	97	76
Barlín (12)	498	Blue dye	Cervix	81	51
Desai (21)	120	Blue dye	Cervix	86	52
Vidal (22)	66	Blue dye	Cervix	62	35
Mais (23)	34	Blue dye	Cervix	62	NA
Lopes (24)	40	Blue dye	Corpus	78	NA
Farghalli (33)	93	Blue dye	Corpus	73,1	NA
Tornè (27)	74	Technetium	Corpus	74	19
Solima (26)	59	Technetium	Corpus	95	NA
Favero (32)	42	Technetium	Corpus	73	NA
Holloway (25)	35	Blue dye + ICG	Cervix	100	100
How [*] (28)	100	Blue Dye or Patent Blue + ICG + Tc	Cervix (submucosal + deep)	92	76
Sawicki [*] (29)	188	Radiocolloid + Blue Dye or Blue dye	Cervix+ Corpus Cervix + Corpus	90,9	72,5

^aThis study presents separate results for 2 different injection sites (cervical and corporeal) therefore we divided their results in this table by injection site for relevance. Note: Corporeal injection: 30 patients had Technetium only; Cervical injection: 1 patient had Technetium only.

^bTranscervical injection to isthmocervical junction, considered "deep cervical".

^cIn this study a dual cervical injection was performed: submucosal + deep.

^{*}The two studies from How et al and the two from Sawicki et al referred to different population. Therefore they have been all included

mapping. Para-aortic SLNs are found more often using corporeal and deeper (3–4 cm) cervical injection techniques. Isolated para-aortic SLNs are uncommon. Studies in which the protocol includes a systematic para-aortic lymphadenectomy have a higher rate of detecting para-aortic SLNs, as well as isolated para-aortic metastases^(24, 27).

Finally, regarding ultrastaging we observed a broad difference of protocols among different centers and clear guidelines for SLN ultrastaging have not been established in gynecologic pathology.

DISCUSSION

At present, even if recently the National Comprehensive Cancer Network acknowledged the use of SLN mapping for endometrial cancer as an acceptable option for surgical treatment⁽⁴¹⁾, the role of SLN biopsy in endometrial cancer is less clearly defined than in breast cancer, melanoma, or early stage vulvar and cervical cancers. Optimal timing of injection, best site of injection and the most appropriate tracer material are still being actively investigated. Three important features on the role of SLNM in EC deserve to be addressed.

First, three different types of SLN mapping techniques exist based on site injection: uterine subserosal, cervical and endometrial via hysteroscopy.^(42, 43)

Second, in the last years different methods have been implemented for improving delineation of lymphatic drainage. Since 1996, blue dye with or without technetium, has been the predominant dye used to identify SLNs⁽³⁹⁾. Detection rates of approximately 80 % have been reported in literature. However, the results do not reflect bilateral detection rates which are the most clinically relevant as the lymphatic drainage in the pelvis is not unilateral⁽⁴⁴⁾. When looking at bilateral rates the bilateral mapping occurs in approximately half of the cases. This means that approximately half of the patients would still need a form of lymphadenectomy and bilateral detection rates need to see improvement. Near Infrared (NIR) fluorescence with indocyanine green (ICG) has been described for SLN mapping in several types of cancer with promising results in terms of detection rates, NIR imaging appears to provide beneficial techniques for SLN mapping in gynecologic malignancies. NIR imaging capabilities are now available for the da Vinci SI robotic platforms as well as for laparoscopic and open approaches (PINPOINT and SPY Elite). Small single series have been already published^(25, 38, 45) and

ongoing studies are trying to assess the detection rate of SLNs for gynecological cancers using ICG and NIR fluorescent imaging⁽⁴⁶⁾.

Third, in many centers for SLNs enhanced pathology assessment is performed if the initial H&E is negative. Ultrastaging involves additional sectioning and staining of the SLN with H&E and immunohistochemistry (IHC) to examine the SLN for low volume metastatic disease⁽⁴⁷⁾ including micro-metastases (MMs) and isolated tumor cells (ITCs)⁽⁴⁸⁾. The role of MMS and ITC has not yet been defined and needs to be addressed. In fact, due to the implementation of ultrastaging during SLN mapping procedures, a growing number of patients will be diagnosed with ITCs and MMs in comparison with patients undergoing conventional procedures.

Finally, as SLN mapping for EC is gaining acceptance, a larger number of patients will undergo SLN removal without a full lymphadenectomy. The management of these patients needs to be addressed and the role of a second surgical step for patients with positive SLNs should be studied. In patients with endometrial cancer, techniques in SLN mapping/biopsy continue to evolve. Advancements in surgical treatment approach, staging, and technology have led to decreased false-negative rates and improved detection rates. Complete or selective pelvic and para-aortic lymphadenectomy remains the standard of therapy for now, as surgical staging is the most important prognostic factor in this group of patients; however, SLN mapping is rapidly gaining ground. This authoritative acknowledgment will likely influence standards of care for women with endometrial cancer around the world. The body of evidence for results with this new standard will expectedly increase.

An optimal route of tracer administration is a principal question related to the use of SLN mapping in endometrial cancer, followed by the choice of the tracer and the issue related to the corrected timing of the injection.

Lymphatic mapping using SLN biopsy through intraoperative injection of a mixture of blue dye, ICG, and radioactive technetium into the cervix appears to be feasible and convenient, and provides good results in patients with endometrial cancer. Indocyanine green is demonstrated to be superior to blue dye and comparable to 99mTc-SC in terms of SLN mapping. A combination of ICG and 99mTc-SC has a high detection rate of SLN, resulting in fewer complete lymphadenectomies and their associated morbidity. Due to satisfactory detection rates with ICG and 99mTc-SC, blue

dye may not be essential to SLN detection in endometrial cancer. Large multi-institutional randomized studies comparing SLN mapping to comprehensive lymphadenectomy in endometrial cancer will be required to confirm the excellent negative predictive values and high sensitivity for detection of disease.

Sentinel lymph node mapping for endometrial cancer balances the need to assess nodal disease with the low likelihood of nodal metastasis for

most patients. It is a technique with minimal morbidity, sparing the endometrial cancer patient a more involved operation. Therefore, we believe this technique will be utilized by an increasing number of gynecologic surgeons in the future.

Achieving high bilateral SLN detection rates and low false-negative rates is mandatory to implement the SLN mapping as a routine component of clinical practice.

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