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Sentinel lymphnode for endometrial cancer: where are we?

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ABSTRACT

Endometrial cancer (EC) is the most common cancer of all gynecological malignancies. Most women are diagnosed with an early-stage disease, which generally has a good prognosis. Lymph node dissection represents a cornerstone not only for staging but also for treatment of EC.

In recent years a novel technique "Sentinel lymph node (SLN)" emerged as a valuable alternative option to lymphadenectomy. This technique has in most of the literature reports a reduced morbidity and enhanced detection of metastatic disease, due to contribution to detection of aberrant lymphatic pathways on one hand, and improvement of pathologic ultra-staging techniques on the other hand.

The current review aims to summarize the existing data on the feasibility of the SLN technique and the oncologic outcomes.

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Introduction

Endometrial cancer (EC) is the most common gynecologic cancer. Most women are diagnosed at an early-stage disease according to International Federation of Gynecology and Obstetrics (FIGO), the stage I [1, 2].

Ten to 15% of these patients will have a metastatic nodal disease, the nodal status being a significant prognostic factor for evolution [3, 4]. The presence of Metastatic nodes is correlated with a significant decrease in overall survival (OS) and disease-free survival (DFS). The five-year DFS is 90% in the absence of lymph node metastases (LNM); it decreases to 75% when the pelvic nodal metastases are present, and 38% in the case of paraaortic metastatic nodal metastases [4, 5].

Lymphadenectomy remains the gold standard for the staging of the EC; however, its therapeutic benefits are still controversial [6-8]. For this reason, some authors have considered the less morbid possibility of staging "SLN".

The SLN procedure allows for avoiding systematic LND. It also identifies aberrant lymphatic drainage pathways of the uterus [9]. An additional benefit of the SLN mapping is that it is more accurate in the detection of micrometastasis by the improvement of pathologic ultra-staging methods [10].

The current literature review aims to determine the feasibility and oncologic outcomes of the SLN mapping in the surgical management for stage I of EC.

Discussions

1. Feasibility

a) Technique

Bonneau et al. found out that the sensitivity value was 100% when a cervical injection is performed compared to 75-100% and 50-100% for endometrial and myometrial injections, respectively [4].

The combined technique consists in the injection of 1ml of 1mCi of Tc99 in the cervix at 3 and 9 o'clock positions, either 18 hours before the surgery in the nuclear medicine department or in the operating room with the blue injection [11-14].

In the first case, preoperative lymphoscintigraphy or dynamic imaging (three-dimensional single-photon emission computed tomography with integrated CT; SPECT CT) is conducted allowing to guide the LND specifying the number, localization and atypical drainage of SLNs [4, 15-17]. A gamma-detecting probe is then utilized intraoperatively to discriminate « hot » areas identified by an increased uptake of the signal [18-22].

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Indocyanine green (ICG) represents an alternative to the first techniques for lymphatic mapping in EC [1, 23-25]. The injection is performed in the same sites as described in the first method. On the other hand, specialized near-infrared imaging equipment is required.

b) Sensitivity and false-negative rate of the SLN procedure

Rossi et al. reported a SLN' sensitivity of 97.2% (95% CI 85.0–100), a negative predictive value (NPV) of 99.6% and a false negative (FN) rate of 3% [2]. The only FN case was obtained in a high grade (serous) cancer [2].

The FIRES trial is a multicenter cohort prospective study that enrolled 385 patients with stage I of EC. All the patients received a cervical injection of ICG and underwent SLN mapping followed by pelvic LND with or without para-aortic LND. They concluded that the SLN approach is equivalent to lymphadenectomy in the surgical management of EC, due to its high sensitivity and negative predictive value [2].

In a study conducted by Abu Rustum in 2009, the sensitivity of the SLN approach was 100% and there were no FN cases [19]. Similarly, different studies have also reported a sensitivity value of 100% [20, 21, 26-28]. In another study by Holloway et al, we reported that the SLN group is associated with a higher node metastasis (30.3% vs. 14.7%, p<0.001) and that the FN rate of the SLN procedure was of 2.8% [22, 23, 29-32]. However, Holloway et al. mentioned that the risk of presenting a FN SLN is more apparent when we failed to obtain bilateral detection of SLNs [16]. Barlin et al. demonstrated that the FN rate decreased from 15 to 2 % when we performed a lymphadenectomy in the hemipelvis, where no SLN was displayed [24]. It has been shown that the SLN procedure allows identifying atypical lymphatic drainage pathways of the uterus [9, 33-36]. They showed that 5% of SLNs are identified in the presacral area and deep internal iliac region [9].

Barlin et al. demonstrated the importance of applying the SLN mapping algorithm [22]. The first step consists of a peritoneal and serosal evaluation and washing. Then, a retroperitoneal evaluation is conducted in which the mapped SLN, as well as any suspicious nodes regardless of mapping, are excised. In the absence of mapping in a hemipelvis, a side-specific LND should be performed [37-40].

When the NCCN algorithm was followed, the SLN procedure accurately displayed metastatic lymph node [23, 24].

Besides, the society of gynecologic oncology (SGO) considered that applying the SLN surgical algorithm is a reasonable staging strategy that provides information on nodal metastasis and potentially decreased morbidity with apparent uterine confined EC [25].

In the meta-analysis conducted by Lin et al., a pooled sensitivity was of 91% (95% CI: 87–95%), an overall detection rate of 83 % (95% CI: 80–86%) and a bilateral detection rate of 56% (95% CI: 48–63%) [1]. These results showed that the SLN mapping represents an acceptable approach with an accurate value in the diagnosis of metastatic lymph nodes in EC.

Table1. Sensitivity, Negative Predictive Value (NPV) and False Negative (FN) rates of SLN.

Study	Sensitivity	NPV	FN rate
EC Rossi et al [2]	97,2%	99,6%	3%
Abu Rustum et al [29]	100%		0%
Kim et al [10]	98%	100%	
Bats et al [30]	100%	100%	
Ballester et al [31]	84%	97%	
Holub et al [32]	89%	99%	
Touhami et al [33]	97%	99%	
Holloway et al [18]	98%	99%	
How et al [34]	90%	99%	
Barlin et al [22]	85,1-98,1%	98,1-99%	1,9%
Soliman et al [35]	95%		1,4%
Lin et al [1]	91%		
Ansaril et al [26]	89%		
Holloway et al [36]	97,2%		2,8%
Soliman et al [37]	100%		4,5%

c) Overall and bilateral detection rates

Several studies demonstrated that better results were obtained when the mapping was performed using patent blue with radiocolloid tracer than patent blue alone [4]. How et al. showed a bilateral detection rate of 60% and an overall detection rate of 88% when using radiocolloid and blue dye [14]. Ballester et al. showed that using both radiotracer and blue dye was able to increase the detection rate to 94% compared to 57% when the blue dye is used solely [40].

Frumovitz et al. illustrated that the combined technique detected bilateral SLN in 31% of patients [13]. Leucuru et al. reported a bilateral display rate between 46 and 87% when the combined technique is carried out [41, 42].

Nonetheless, other authors reported a higher detection rate ranging between 55 to 60% when patent blue is used solely [38, 39].

A meta-analysis conducted by Smith et al. reported that blue dye alone detected at least one SLN in 80% of women and bilateral SLNs in 50% of them, and that the Combined method increases the detection rate of at least one SLN to 88% but not the bilateral rate detection which was of 51% [43].

Lecuru et al. reported a detection rate ranging from 45 to 100% when the combined method is performed [42]. However, Lin et al reported an overall detection rate of 86% (95% CI: 83–89%) and a sensitivity of 93% (95% CI: 87–96%) when blue dye is used [1]. In the same study,

combining patent blue to radiotracer showed the same detection rate of 86% (95% CI: 82–90%), and a sensitivity of 92% (95% CI: 84–96%) [1].

Concerning the ICG, some authors considered it as the most effective method in the detection of pelvic SLN [43-45].

Lin et al. showed that the use of ICG is characterized by a high bilateral detection rate: 78% (95% CI: 72–84%) and overall detection rate: 93% (95% CI: 89–96%) [1]. In the FIRES trial, the overall detection rate was 86% when using ICG dye [2, 46-48]. In another study conducted by Abu Rustum et al. it has been shown that the detection rate increased from 77 to 94% (p=0.03) within a 30-case experience [49].

Furthermore, Ruscito et al. reported that ICG SLN mapping has similar overall detection rates compared to the Tc99 combined with the blue dye technique. Similarly, they did not find any difference in bilateral detection rates between ICG and blue combined to Tc [50]. When comparing ICG to the blue dye alone, similar results were found in the overall detection rate, while an increase in the bilateral detection was shown when using ICG [50]. Some other series demonstrated that ICG increased the frequency of SLN detection compared to blue dye [34, 45]. Frumovitz et al. found that the detection of at least one SLN, when using ICG and blue dye, is for 96% and 74% of patients, respectively [13].

2. SLN pathology

Ultra-staging consists of cutting additional sections and applying immunohistochemistry (IHC) staining [10].

It improves the detection of the micrometastatic disease, identifying more micrometastasis and isolated tumor cells (ITC) [2, 3, 51]. Also, the evaluation by IHC increases the probability of identifying small-volume disease compared to the standard coloration by hematoxylin-eosin (HE) [10, 52-55]. Several studies found out that 50% of metastatic lymph nodes was represented by low-volume tumor cells, identified by ultra-staging processing [10, 56-62]. Abu Rustum et al. noted 11% positive nodes in this low-risk group of EC, mostly recognized by ultra-staging techniques [29, 63-65].

In the Senti-Endo study, authors found out macrometastases in 50% of the cases, micrometastases in 44%, and ITC in 6% [60, 66, 67]. They also demonstrated that IHC allows rectifying the diagnosis of positive lymph nodes that are unrecognized by the standard HE in 47 % of cases [60]. Bosquet et al. assessed that the rate of occult micro-metastasis was 12.5% after IHC staining [68]. Other studies showed that ultra-staging procedure allowed to double the number of metastatic nodes found, compared to those identified by the routine HE (mostly by the detection of micro-metastases and ITC) [31, 36]. Furthermore, Bernardin et al. concluded that IHC increased the sensitivity and the NPV of the SLN to 83.3% and 93.8%, respectively, compared to those of routine HE which are 33% and 79%, respectively [69-71].

Yabushita et al. demonstrated that missing the detection of those low-volume tumor cells represents a risk factor for recurrence in EC [64]. Similarly, in a study conducted by St Clair et al. we noted that the recurrence-free survival at 36 months was 71% for macrometastases, but it was 86% for both micrometastases and ITC [65].

Moreover, Kim et al. concluded that the ultra-staging of SLN may be omitted if there is no myometrial invasion on the final pathologic result, as also noted that micrometastases and ITC were more frequent in EC with myometrial invasion on the final examination [10].

Table 2. Overall and bilateral SLN detection rates

Study	Blue		Blue+Tc		ICG	
	Detection rate	Bilateral detection rate	Detection rate	Bilateral detction rate	Detection rate	Bilateral detction rate
Frumovitz et al [13]		31%				
Holloway et al [47]	76%	40%				
Ballester et al [40]	57%		94%	62%		
How et al [14]			88%	60%		
Vidal et al [38], Eitan R et al [39]	55 – 60%					
Touhami et al [33]			94%	74%		
Bats et al [30]			70%	37%		
Barlin et al [22]			81%	51%		
Khoury Collado et al [27]				67%		
Lecuru et al [42]				46-87%		
Rossi [2]					86%	52%
Rossi [51]					88%	60%
Lin et al [1]	86%		86%		93%	78%
Khoury Collado et al [49]					77-94%	
Ansari et al [26]					77,8%	
Soliman et al [35]					89%	

3. Complications

Some specific complications occurred when the blue dye is used, most frequent encountered being allergic reactions in 0.14 – 3% of the cases [3]. For instance, we can mention erythema, urticaria, swelling, oxygen desaturation and anaphylactic shock [1]. Patent blue will also cause blue-green-colored urine during 24 hours postoperatively [1, 3].

Unlike the blue dye, the high cost of Tc99 which requires nuclear technicians, physicians and the maintenance of the radiation probes represents considerable disadvantages [13].

On the other hand, specialized near-infrared imaging equipment is required, representing the principal disadvantage of the ICG use [18].

It is important to mention that the bright green effect on neared imaging may lead to the removal of adipose tissue or lymphatic trunks instead of mapped lymph nodes [13]. For instance, in the FILM trial, this occurred in 5 to 6% of presumed nodes which were not confirmed as nodes on pathology [13].

Secondly, this bright signal also conduced to the excision not only of the true SLN but also of the nodes in second or third echelon, which cannot be seen with blue dye [13].

4. Oncologic outcomes

Women with stage I of EC had an excellent survival rate with a recurrence rate of less than 10% [53]. Fifteen percent of patients who relapsed had positive lymph nodes [54]. Metastatic lymph nodes are correlated with decreased overall survival (OS) and disease-free survival (DFS) [11, 15]. Morrow et al. reported that the 5-year DFS was 90% when there were no positive nodes, 75% with positive pelvic nodes and 38% with metastatic para-aortic nodes [54, 72].

A cochrane systematic review, comparing stage I patients of EC who either had or who had not undergone lymphadenectomy, found out that the OS was similar HR = 1.07 [IC 95%: 0.81-1.43]), as well as the DFS (HR = 1.23 [0.96-1.58]) [57]. They also concluded that the rate and localization of recurrences are the same in both groups [57]. Benedetti et al found that lymphadenectomy identified 10% more cases of metastatic lymph nodes, but with no survival benefits [7]. They reported a 5-year DFS and OS rates of 81.7% and 90%, respectively, when no lymphadenectomy was performed, compared to 81 % and 85.9%, in the group of lymphadenectomy [7].

The ASTEC trial had also come to the same conclusion of the absence of survival benefit and the increase of morbidity when lymphadenectomy was performed [6, 73]. Besides, Kitchener et al studied the efficacy in the realization of lymphadenectomy in an early stage of EC and did not notice any advantage in OS, recurrence-free survival and disease-specific survival [6].

However, other studies compared retrospectively patients with EC who underwent lymphadenectomy with those who did not underwent it, and concluded that lymphadenectomy was associated with increased survival in the intermediate or high-risk group of EC [58, 59]. In light of these data, some authors have considered the need for a less morbid technique that could allow relatively similar staging capabilities as lymphadenectomy.

NCCN guidelines have advocated for the SLN procedure in the staging of EC, and considered it as a level 2B evidence [2]. Besides, and as seen in the previous chapters, the SLN mapping allowed the detection of more positive nodes, had more upstaged IIIc disease and then got more adjuvant treatment [36].

Raimond et al. concluded that SLN mapping allowed to recognize 10% more positive lymph nodes, and this permit to lead up to an adequate adjuvant treatment [52]. How et al demonstrated that the recurrence in the hem-pelvis, where the SLN biopsy and lymphadenectomy were performed, was reduced by 68 % compared to the group of lymphadenectomy (HR 0.32, p=0.007) [61]. Besides, some studies showed that metastatic disease occurred in non SLNs in 40% of women [47, 62].

Moreover, « occult » metastases identified as a result of the enhanced pathologic techniques of ultra-staging may increase the risk of recurrence in patients with early-stage of EC, if not detected with conventional techniques [4, 64]. In a study conducted by Yabushita et al. authors noted that the probability of recurrence was positively associated with the presence of micro-metastases, independently of the stage of the tumor [64]. Kim et al. reported that the identification of low-volume disease may be essential for the follow-up and the adjuvant treatment [10]. Clair et al did not find a difference in the recurrence rates between patients with micro-metastasis treated by adjuvant treatment and those without metastases [65].

Schiavone et al. studied the surgical management of carcinosarcoma and compared SLN mapping to lymphadenectomy [66]. They reported that the median number of metastatic nodes was comparable between both groups (p=0.2 and observed no difference in median progression-free survival between the two groups (23 vs. 23.2 months, respectively; p=0.7) [66]. Moreover, Schiavone et al. also studied serous uterine carcinoma, and compared SLN mapping to routine lymphadenectomy [67]. They did not reach a difference between both groups, neither in the two-year progression-free survival (77% vs.71%, respectively, p=0.3) nor in the adjuvant therapy [67].

Thus, NCCN guidelines suggested the possibility of applying the NCCN algorithm in women with high-risk group of EC [18].

Conclusions

Endometrial cancer (EC) is the most common cancer of all gynecological malignancies.

The current literature data sustain that the SLN procedure represents a feasible and reliable approach in the early-stage of EC.

We assume that it is time for patients with early-stage EC to undergo the SLN procedure following the NCCN algorithm. It helps to reduce morbidities related to unnecessary LND, and ensures a more comprehensive care including surgery and adjuvant therapy.

However, future prospective randomized trials are needed to accurately identify oncological outcomes when applying the SLN procedure to women with EC, and to give a higher degree of recommendation to the NCCN algorithm.

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