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Review

Sentinel lymph node biopsy in endometrial and cervical cancer: current and controversial issues

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Summary

The authors review the controversial issues regarding the management algorithms, the impact of ultrastaging to adjuvant treatment, and outcomes from the role of sentinel lymph nodes (SLN) in endometrial cancer (EC) and cervical cancer (CC). According to standard recommendation, side specific nodal resection is required in case of failed mapping. Alternative algorithms were proposed to reduce overtreatment in low risk EC and CC. The positive results of new algorithms may lead to a proper selection of patients in which pelvic lymphadenectomy could be avoided. Ultrastaging had an impact on accuracy by increasing the detection rate by 25-50%. Occult LN metastasis was associated with myometrial invasion in EC, but the relationships between other known factors of CC recurrence are unclear. Prognosis for the patient with either EC or CC in SLN algorithm group was similar to those in the lymphadenectomy group while the latter group had shown a higher surgical morbidity.

Key words: Algorithm; Cervical cancer; Endometrial cancer; Outcome; Sentinel lymph node; Ultrastaging.

Introduction

In gynecological cancers, the application of the sentinel lymph node (SLN) procedure has been investigated in vulvar, cervical, and endometrial cancer (ECs). This technique provides potential advantages over complete staging and also decreases both short- and long-term surgical complications. Several well-designed studies have been able to demonstrate feasibility with the high detection rates and low false negative rates. However, the optimal management and survival benefits associated with SLN biopsy, as well as the significance of immunohistochemistry (IHC) detecting micrometastases have yet to be determined. This review's aim is to discuss these topics with updated information on the following: 1) recommendations and alternative algorithms, 2) role of ultrastaging and adjuvant therapy, and 3) the impact of SLN mapping on patient outcomes.

Recommendations and alternative algorithms

EC

According to National Comprehensive Cancer Network's (NCCN; version 1.2018) guidelines, SLN mapping may be considered in the selected patients and may also be used in high-risk histologies (serous carcinoma, clear cell carcinoma, and carcinosarcoma) [1]. The SLN algorithm for surgical staging is based on the prospective database study of Barlin *et al.* After applying the algorithm, the false-negative rates dropped to 2% [2]. The surgical algorithm is as follows: 1) peritoneal and serosal evaluation and washings, 2) retroperitoneal evaluation including excision of all mapped SLNs and suspicious nodes regardless of mapping, and 3) if there is no mapping on a hemi-pelvises, a side-specific pelvic, common iliac, and interiliac lymph node dissection (LND) is performed. Para-aortic LND is performed at the attending physician's discretion. The key point to successful SLN mapping is the adherence to SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping [1].

Sinno *et al.* proposed an alternative algorithm, the "Reflex Frozen Section" strategy, to allow similar detection of lymphatic metastases with a significantly lower rate of lymphadenectomy when compared with a standard algorithm. The 114 women with complex atypical hyperplasia and grade 1-2 EC underwent SLN mapping using a cervical injection with isosulfan blue or indocyanine green (ICG). The SLN assessment was followed by a total hysterectomy and bilateral salpingo-oophorectomy. If SLNs were identified in both hemi-pelvis, a uterine frozen section was omitted. Frozen section was performed only for failed bilateral mapping. Side-specific lymphadenectomy was performed only if high-risk features were identified (defined as a grade 3 tumor, outer half myometrial invasion or tumor > 2cm in

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Table 1. — *Sentinel node studies with ultrastaging in endometrial cancer.*

Author	No. of patients	Route of surgery	Tracer	Detection rate (%)	Bilateral detection rate (%)	Percent of STN detected based on ultrastaging
Ballester *et al.*, 2011 [9]	111	Laparoscopy laparotomy	Tc, B	89	52.5	50%
Khoury *et al.*, 2011 [10]	226	Robotic laparoscopy laparotomy	B	84	67	25%
Desai *et al.*, 2014 [11]	120	Robotic assisted	B	86	52	50%
Naoura *et al.*, 2015 [12]	180	NR	Tc+B	88	63	41%
How *et al.*, 2015 [14]	100	Robotic assisted	Overall	92	76	33%
Hagan *et al.*, 2016 [13]	108	Robotic assisted	ICG	96	78	25%
Paley *et al.*, 2016 [15]	123	Robotic assisted	ICG	96.7	80	44%
Sinno *et al.*, 2016 [3]	114	Robotic assisted	ICG	86%	62.3%	37%
Lui *et al.*, 2017 [15]	166	laparoscopy	ICG	95.4	74.5	31%

B = blue dye; ICG = indocyanine green; Tc = technetium.

diameter). This approach resulted in lower lymphadenectomy rates for the new algorithm as compared to the standard protocol (9.2% *vs.* 36.8%, $p = 0.04$) without reduction of LN metastases [3].

Based on these results, Tanner *et al.* have transitioned to utilize this new mapping algorithm within academic programs for 113 women with low-grade EC. High-risk uterine features were identified in 8 of 21 (38%) patients who failed SLN mapping. Side specific and overall pelvic lymph node dissection (PLND) rates of patients in this group were 5.3% and 7.1%, respectively. If the NCCN guideline algorithm was used, side specific and overall PLND rates would have been 12.4% and 18.6%, respectively. These results are significantly higher than found in Reflex Frozen Section assays ($p = 0.02$ and $p = 0.01$) [4]. The advantage of this algorithm is likely to be greater for non-experienced centers or hospitals without access to fluorometric imaging equipment in which bilateral SLN detection rates remain low.

Cervical cancer (CC)

Comier *et al.* proposed the SLN mapping algorithm for early-stage CC which includes the following: 1) SLNs are removed and submitted to ultrastaging, 2) any suspicious LN is removed regardless of mapping, 3) if only unilateral mapping is noted, a contralateral side-specific pelvic LND is performed (including inter-iliac nodes), and 4) parametrectomy en bloc with primary tumor resection is done in all cases. This algorithm could accurately detect all patients with LN metastasis (false negative rate 0%) while eliminating the need for complete bilateral lymphadenectomies in 75% of this group [5]. As the SLN in the presacral area has been noted in some studies, they should be included in a side-specific lymphadenectomy when an ipsilateral approach has failed. Parametrial SLNs are difficult to identify especially when using blue dye or radiocolloid as tracers. This study found one case with parametrial nodes positive had tumor size of only 1 cm. They recommend exercising caution when abbreviating of parametrectomy and performing a parametrectomy in all cases. Base on the results of this study, the National Comprehensive Cancer Network (NCCN) considers SLN mapping as part of the management of select Stage I CC and emphasized that the key to successful SLN mapping is adherence to the SLN algorithm. Parametrectomy is an exception for Stage IA1 with no LVSI within the NCCN guideline [6]. To meet this algorithm, approximately 25% of women with early stage CC need to undergo, at the least, a unilateral LND. Fagotti *et al*. have proposed a new modified SLN surgical algorithm that could reduce the rates of complete lymphadenectomies. They found that no patients with a tumor diameter less than 2 cm, squamous and adenosquamous histotype, and negative MRI nodal assessment, had lymph node metastases. This group of women was named as a very low-risk group (VLRG). Two alternative algorithms were assessed. The first one was VLRG selection after SLN, this kind of approach provides benefits in the subset of patients in which optimal SLN detection failed, avoiding unnecessary LND. The second was VLRG selection prior to SLN. This approach avoids more cases of a SLN procedure which may decrease the chances to correctly stratify risk categories. On the other hand, it could decrease operative time, the surgical costs, and ultrastaging [7]. A prospective clinical trial of 463 patients provided a more reliable result of this approach. No LNM was detected among 161 (34.8%) patients who met the criteria of VLRG. This result leads to proper selection of patients in whom SNL could be avoided [8].

Role of ultrastaging and adjuvant therapy

EC

The classification of such small tumor deposits was adopted from breast cancer classifications and three categories are recognized: macrometastasis (2 mm or more), low-volume disease which encompasses micrometastasis (LNmM: < 2mm and > 0.2 mm), and isolated tumor cells (ITCs: 0.2 mm). The majority of ultrastaging [Hematoxylin-Eosin staining (H&E) + IHC] are low-volume metastases which increases overall detection of node metastases. Table 1 shows the percentage of STN detected from ultrastaging of large studies (n > 100) [3, 9, 16]. It could increase the detection of node metastases 25-50%.

Table 2. — *Prognostic impact of occult LN metastases in endometrial carcinoma.*

Author	No. of patients	Stage	Percent of patients (per total patients)				Percent of patients receiving adjuvant therapy (%)	Outcome	Median FU (months)
			N	ITC	MM	Macro			
Clair *et al.*, 2016 [23]	844	IA-IIA	89.2	2.7	2.5	5.6	N/ITC/MM/Macro 14/83/17/89	**3YRFS** - N: ITCs: MM: Macro 90%:86%:86%:71% ($p < 0.001$)	26
Plante *et al.*, 2017 [24]	519	IA-IVB	83.6	6	2.1	8.3	**CMT** - ITC:MM:Macro 35.5:72.7:83.7 **RT-** ITC:MM:Macro 45.2:54.5:67.4	**3YPFS**- N: ITCs: MM: Macro 87.6%:95.5%: 85.5%:58.5% ($p = 0.0012$)	29
Todo *et al.*, 2016 [25]	61	I-II with at least one of recurrence risk	85.2	9.8	4.9	0	N/ ITC+MM 64/88	**Recurrent rate-** ITC/MM: N HR 17.9 (95%CI: 1.4-232.2) **8YOS** - ITC/MM: N 71.4% *vs.* 91.9% ($p = 0.074$) **RFS** - ITC/MM: N 55.6 *vs.* 84% ($p = 0.06$) **Time to recurrence -** ITC/M *vs.* N 49 *vs.* 16.5 months ($p = 0.08$)	107

CMT: chemotherapy; ITC: isolated tumor cells; MM: micrometastases node; macro-macrometastases node; OS: overall survival. RFS: recurrence free survival; RT: radiotherapy.

Table 3. — *Percentage of micrometastases, lymph node detection. and prognostic impact.*

Author	No. of patients	Stage	Adjuvant therapy	Micrometastases lymph node (%)	Prognostic impact (presence: absence LN MM)	
					OR or HR	*p* value (95%CI)
Lentz *et al.*, 2004 [27]	132	IA2-IB2	NR	15%	NR	NR
Stany *et al.*, 2015 [28]	129	IA2-IB2	RT 22% CMT 13%	20%	PFS: HR 1.07 OS: HR 1.09	0.93 0.91
Colturato *et al.*, 2016 [29]	83	Ib1-IIA	0%	7%	RR: OR 11.73	0.01 (1.57-87.8)
Cibula *et al.*, 2012 [30]	645	IA-IIB	33%	10.1% (ITC 4.5%)	RFS: HR 3.15 OS: HR 6.86	0.18 (0.73-5.14) 0.002 (2.09-22.6)
Horn *et al.*, 2008 [31]	281	IB-IIB	NR	22.2%	RFS: 68.9% *vs.* 91.4% 5YOS: 63.8% *vs.* 86.8% OS: RR 2.5	< 0.0001 (55.5-82.4) < 0.0001 (50.9-76.7) 0.0002 (1.5-4.0)

CMT: chemotherapy; HR: hazard ratio; ITC: isolated tumor cells; MM: micrometastases node; macro-macrometastases node; NR: no report; OR: Odds ratio; OS: overall survival; PFS: progressive free survival; RFS: recurrence free survival; RT: radiotherapy.

Algassen *et al.* found that IHC staining detected significantly more metastases when compared to H&E staining. This had an impact on the diagnostic accuracy of the sentinel concept. Sensitivity was reduced from 66.7% to 33.3% and the negative predictive value fell from 94.7% to 79.0% only when the non-sentinel lymph nodes (NSLNs) were additionally IHC stained. Contrarily, if the SLNs were also IHC stained, the sensitivity rose to 83.3% and the NPV rose to 93.8% [17]. Recent studies have shown that ultrastaging upstaged 10% of patients with presumed low risk and 15% of patients presumed intermediate risk [18]. Cibula *et al.* reviewed that 87% of patients with ultrastaging detection had some degree of myometrial invasion while only 0.8% in those with no myometrial invasion [19]. The result of the Kim *et al.* study also supports the incorporation of pathologic ultrastaging of STNs with any degree of myoinvasion [20]. In this study, ultrastaging detected an additional 23 (4.5%) of the 508 patients with low-volume metastasis. Of the 198 patients with superficial myoinvasion, 16 patients (8.0%) were found to have low-volume disease. This is in contrast to the much lower rate of low-volume ultrastage detected nodal disease found in only two (0.8%) of 242 cases with no myoinvasion on final pathologic examination. Erkanli *et al.* found a worse overall survival (OS) and recurrent free survival (RFS) in the patient with isolated micrometastases. However, 86% of these patients had high-

risk uterine factors [21]. McCoy *et al.* found only two cases of micrometastases in 51 patients with endmometrioid Stage I (1.3%). Both patients had adjuvant radiation therapy for uterine high-risk factors [22].

Ultrastaging in cases without uterine factor may not be necessary. At this time, the clinical significance is unclear and requires further studies. Table 2 shows the studies of prognostic impact of occult LM metastases in EC [23-25]. Clair *et al.* reported that the EC patients with isolated tumor cells and micrometastasis had improved oncological outcomes in comparison to those with macrometastasis to the lymph nodes. There were 844 patients who underwent staging with SLN mapping for EC with 44 (5.2%) patients who had low-volume metastasis; 23 (2.7%) who had ITCs alone, and 21 (2.5%) with micrometastases. The patients with isolated tumor cells and micrometastasis frequently received adjuvant chemotherapy. Adjuvant treatment, including chemotherapy, was given in greater than 80% of these cases. The three-year, progression-free survival for patients with ITCs or micrometastasis was 86%, compared with 71% for those with macrometastasis ($p = 0.001$) [23]. In one study conducted by Todo *et al.* nine of 61 EC patients had occult LN metastasis, comprising of six ITCs and three LNmMs. Eight of nine (88%) had received either radiation or chemotherapy. The percentage of patients receiving adjuvant treatment in the node-negative group and occult metastases were 64% and 88%, respectively. The patients with ITCs or LNmMs had lower OS and RFS than node-negative patients. Statistically significant results were not achieved and this might be explained by the small number of subjects in the study [25]. This study did not distinguish between those with ITCs *vs.* LNmMs. Plants *et al.* evaluated on the outcome of patients within the ITCs group only and found that these patients had excellent outcomes. They concluded that patients with ITCs and low-risk uterine disease may not require adjuvant treatment [24]. Further studies with the prospective trial are imperative to demonstrate the survival benefits of ultrastaging. At present, the patients with micrometastases should be treated or further observed.

CC

Ultrastaging has been associated with higher overall detection rates when compared with routine H&E alone (95% *vs.* 89.4%) [26] Table 3 shows the detection rate and prognostic impact of LNmM in CC. [27-31]. Lymph node micrometastases (LNmM) were detected in 15% of early-stage CC patients with histology negative lymph nodes and there has been no relationship between LNmM with other known factors of recurrent cervical cancer [27]. A multi-institutional retrospective study followed 129; early-stage CC patients with histology negative lymph nodes. Patients with LNmM were found in 20%. LNmM was not associated with recurrence or the OS rates nor was it associated with any other high-risk clinical or pathologic variables that predict recurrence [28]. On the other hand, some studies indicated that LNmM was associated with worse survival rates. Horn *et al.* found LNmM in 22% of node-positive cervical cancer patients. The patients in this group represented significantly reduced rates in both RFS and the five-year OS when compared to patients without metastatic disease (RFS: 68.9% *vs*. 98.4%, five-year OS: 63.8% *vs*. 86.6% for LNmM and negative nodes patients, respectively) [31]. A large multicenter-retrospective study conducted by Cibula *et al.* reported that macrometastasis, LNmM, and ITC were detected by SN ultrastaging in 14.7%, 10.1%, and 4.5% patients, respectively. Presence of LNmM was an independent prognostic factor for OS. No significance was found with isolated tumor cells [30]. A recent retrospective study found that LNmM and ITC were significantly related to deep stromal invasion. The author concludes that LNmM is an important risk factor for recurrence and the consideration for the adjuvant radiochemotherapy in these patients [29].

To date, the data from previous studies have concluded that ultrastaging increases the detection rates but further studies are needed to examine the effects of LNmM and ITC on the survival outcomes in order to consider the optimal adjuvant treatment.

Impact of SLNB on patient outcomes

EC

Leitao *et al.* utilized a modified nodal assessment that used an algorithm that incorporated SLN mapping. The authors found that the SLN mapping algorithm reduces the need for standard lymphadenectomy and does not appear to adversely affect the rates of Stage IIIC detection [32]. The long-term results of the SENTI-ENDO study in patients with Stage I-II EC following cervical dual injection (Tc+B) after 50 months of follow-up revealed that no differences in the RFS between patients with and without detected SLN. Adjuvant treatment vaginal brachytherapy (VBT), External beam radiation therapy (EBRT), and chemotherapy had been administered based on the risk of the patients according to ESMO guidelines. For 111 patients with detected SLN, EBRT and chemotherapy were performed more frequently in patients with positive SLN [33]. Eriksson *et al.* compared RFS and LN metastases between the SLN approach and the selective lymphadenectomy group. In the SLNB group, SLN mapping was performed by injecting blue dye or ICG into cervical stroma superficial and deep level at 3 and 9 o'clock positions for a total of 4 ml. The oncologic outcome is similar for the SLN algorithm as compared to selective lymphadenectomy. The recurrent rates were 3% (SLN) and 14% (LND) and the three-year DFS rates were 94.9% (LND) *vs*. 95% (SLN) [34].

CC

Lennox *et al.* evaluated that the RFS and short-term mor-

bidity rates of the patient with CC, Stage IA/IB. The two- and five-year RFS of patients between the groups with bilateral pelvic node dissection (BPLND) and bilateral sentinel lymph node biopsy (BSLNB) were not significantly different but, the patient in BPLND group was significantly associated with increased surgical time, blood loss, transfusions, and postoperative infections [35]. The preliminary data from the SENTICOL2 randomized trial compared the surgical morbidity of node-negative patients who underwent BPLND *vs*. BSLNB. No false negatives were identified in the latter group. In the BLSNB group, the surgical morbidity related to the lymph-node dissection was 31.4% and largely and significantly reduced from the BPLND group, 51.5% ($p = 0.004$). The rates of early postoperative neurological symptoms were significantly reduced. (7.8% in BSLNB *vs*. 20.6% in BPLND, $p = 0.01$) [36]. Niikura *et al.* followed patients with CC Stage, Ia1-IIA1, after RHND with BPLND or BSLNB. The median follow-up period was 49 months. They demonstrated that none of the patients with negative SLNs in the BSLNM group had lymph node recurrence in the pelvic cavity and they had lower incidences of extremity lymphedema as compared with patients in the BPLND group (8.7 *vs*. 42%) [37].

Conclusion

The algorithm for SLN biopsy has been modified to decrease the rate of unnecessary lymphadenectomies. Side-specific nodal resection in EC and CC could be avoided in the patients with low risk for lymph node metastasis. This approach not only decreases morbidity from overtreatment, it also decreases operative time and surgical costs. Pathologic ultrastaging improves occult LN metastasis detection in both EC and CC. However, the oncologic significance is unclear and long-term follow ups are required in order to consider the optimal, adjuvant treatment. In both EC and CC, similar results regarding the impact of SLNB on patient outcomes have been reported. Long-term follow-up studies have shown DFS and RR of patients who underwent SLNB and they were not different from those who have undergone bilateral pelvic node dissection.

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