

Emerging role of sentinel lymph node mapping for gynecologic oncology in the new era

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Summary

This study aims to update a review of the recent literature on sentinel lymph node biopsy (SLNB) in common gynecological cancer. Fifty-eight published English-language articles were obtained. Most of the well-designed studies were conducted in the patient with vulvar, endometrial, and cervical cancer, but SLNB data in ovarian cancer is limited. The result of diagnostic accuracy reported a satisfactory with a high detection rate, a high sensitivity, and an acceptable febrile neutropenia (FN) rate in all cancer types. The technique of SLNB in vulvar prefers combined radiocolloid and dye methods. The common technique in endometrial and cervical cancer is laparoscopic or robotic-assisted surgery with cervical indocyanine green (ICG) injection while laparotomy is the most frequently used in studies of ovarian cancer. This evidence supports that SLN mapping could replace the traditional lymphadenectomy in early-stage vulvar, endometrial, and cervical cancer. The result of feasibility and efficacy of this procedure in ovarian cancer is promising but more studies are required.

Key words: Sentinel lymph node; Vulvar cancer; Endometrial cancer; Cervical cancer; Ovarian cancer; Gynecologic cancer.

Introduction

Lymph node involvement is the most important prognostic factor in gynecologic malignancies and associated with the rate of recurrent and survival. Lymphadenectomy is one of standard staging and treatment in the current practice of selected cases of gynecological cancer even the rate of lymph node metastasis in early stage is low. This procedure increases operative time, blood loss, and associated with a long and short-term complication such as nerve injury, lymphocyst, hospital stay, and healthcare cost. Sentinel lymph node biopsy (SLNB) procedure has been studied to decrease morbidity without compromising oncological and surgical outcomes. Many studies in melanoma and breast cancer have shown that SLNB procedures accurately predict lymph node status and are associated with less morbidity [1, 2]. This procedure, therefore, has a place in gynecologic malignancy. It has been investigated in gynecological, vulvar, endometrial, cervical and ovarian cancer. Most medical centers now offer SLNB for early-stage vulvar cancer, endometrial cancer and cervical cancer. This technique was recently introduced and evaluated its feasibility in ovarian cancer in some centers. The objective of this review is to summarize and update the available data

on the SLN concept in gynecological tumors.

Vulvar cancer

In early-stage squamous cell vulvar carcinoma, only 25-35% of patient have lymph node metastases, a significant 65-75% possibly do not benefit from elective inguinofemoral lymphadenectomy (IFL). Moreover, this procedure is associated with short and long-term morbidity consisting of wound breakdown, infection, lymphocele, and lymphedema [3].

Reliability of sentinel node mapping

Levenback *et al.*, were the first to describe the feasibility of intraoperative lymphatic mapping in vulvar cancer cases, using isosulfan blue dye. The SLN was identified in seven of the nine cases. The cases in which SLN was not identified were both midline lesion. There were no positive non-SLNs in the presence of negative SLN [4]. The SLNB procedure has been incorporated in the standard of care for patients with early-stage vulvar cancer since the result of long-term follow up from the large study, GROningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V), was published. The results showed that in patients with T1/2 (< 4 cm), squamous cell cancer of vulva

Revised manuscript accepted for publication August 2, 2018

and negative sentinel node, the groin node recurrence is very low (2.3% in unifocal disease) with an excellent survival rate of 97% at three years. It was concluded that in case of a negative sentinel node, it is safe to omit an IFL [5]. The systematic review conducted by Coven *et al.*, per groin detection rate for SLNB using radiocolloid tracer and blue dye was 87%. The false negative rate with SLNB was 6.4%, and the recurrence rates with SLNB and IFL were 2.8% and 1.4%, respectively. SLNB is recommended for women with unifocal tumors < 4 cm and clinically non-suspicious nodes in the groin [6]. The Cochrane Database of Systematic Reviews assessed the diagnostic accuracy of various technique using traceable agents (technetium only, blue dye only, and combined test). All tests could identify cancer in the groin nodes with good accuracy; sensitivities of all tests were more than 90% and negative predictive value (NPV) was more than 95%. There was little difference in diagnostic test accuracy between the combined tests (sensitivity of 95% and detection rate of 98%) and technetium (sensitivity of 93% and detection rate of 96%). The detection rate of blue dye alone was 82%, lower than other techniques. From clinical consequence estimation, the combined test might reduce the number of women with 'missed' groin node metastases compared with technetium only. Blue dye alone might be associated with more 'missed' cases compared with tests using technetium. Sentinel node assessment with technetium-based tests would reduce the need for IFL by 70% in women with early vulvar cancer [7].

Recommendations

The SLN procedure is recommended in patients with uni-focal squamous cell cancers, less than 4 cm, without suspicious nodes at clinical examination [5]. In most of the protocol, the Technetium-99m-labeled nanocolloid with or without blue dye is the main techniques used. Technetium-99m (Tc-99m) is injected 2-4 hours preoperatively around the primary tumor. A preoperative lymphoscintigraphy aids in anatomically locating the sentinel node. During surgery, a gamma probe is used to confirm the location of SLN. Approximately 3-4 cc of blue dye was injected peritumorally and intradermally within 15-20 minutes of initiating the procedure. A complete IFL is recommended if an ipsilateral SLN is not detected. If ipsilateral SLN is positive, the contralateral groin should be evaluated surgically and/or treated with radiotherapy [3, 8]. Near-infrared (NIR) fluorescent imaging was recently introduced for SLN biopsy in vulvar cancer. Indocyanine green (ICG) fluorescence offers a relatively higher tissue penetrance compared with blue dye or low concentrations of Tc-99m. It provides only one-step procedure while maintaining high sensitivity. The largest study of near-infrared/ICG sentinel technique included 27 patients with primary, unifocal vulvar cancer of less than 4 cm with clinically node-negative groins. Sentinel diagnostic was carried out using Tc-99m, ICG, and patent blue. All sentinel lymph nodes were positive for

ICG, giving a sensitivity of 100%, positive predictive value (PPV) of 91.9% compared with Tc-99m. ICG is a promising approach with similar sensitivity as radioactive Tc-99m [9]. However, because of the limited penetration depth of NIR fluorescence imaging, this tracer is feasible only in lean patients and radioactive tracer remain necessary for preoperative surgical planning and to detect deeper SLNs [3, 10].

There are few limitations of SLNB in vulvar cancer. The patients with multifocal disease, underwent radio(chemo) therapy or large size of the tumor are not suitable for this procedure. The lymph vessels might be damaged and a large tumor size can cause stasis of lymph flow, thus affect the detection rate of procedure [10].

Ultrastaging has been shown to improve the sensitivity in detecting metastatic node [3]. The results from GROINSS-V, showed the additional metastases in non-sentinel nodes in 4.2% of patients with isolated tumor cells in the sentinel node. Although the clinical significance of micrometastases remains unclear, the results from this study also reported that the survival rate of patients with sentinel node metastases larger than 2 mm was lower than with sentinel node metastases 2 mm or smaller. No cut-off size for sentinel node metastasis below which the risk of additional groin metastases become negligible. The author recommended that all patients with sentinel metastases should have additional groin treatment [11].

Endometrial cancer

In early stage endometrial cancer, the benefit of lymphadenectomy is controversial. Recent studies have shown that there is no therapeutic benefit to complete lymphadenectomy. FIGO 2009 staging system still incorporates lymph node status for diagnosis and prognosis. SLN mapping may provide an appropriate middle ground between the complete lymphadenectomy and no nodal evaluation.

Reliability of sentinel node mapping

Sentinel node mapping tends to be a new reference standard which replaces the current gold standard (full lymphadenectomy). This should be based on evidence that the new reference method has the potential to improve diagnostic or staging in a very significant way. Moreover, a false negative rate is imperative to be considered, typically less than 5% is acceptable [12]. From meta-analysis study and SENTI-ENDO study revealed that the overall detection rate (DR) and bilateral detection rate (BDR) were 83-89% and 56%, respectively [13, 14]. The present authors reviewed the studies of sentinel node mapping of endometrial cancer from 2011-2017 which had a number of patients more than 100 (Table 1). Several studies have demonstrated the overall satisfactory efficacy and effectiveness of SLNB. There is no difference of the overall detection rates and bilateral detection rates between studies used robotic-assisted and laparoscopy. The most recent studies used ICG as a

Table 1. — Studies of STN mapping in endometrial cancer (N>100)

Author	Design	time period	No of patients	Histology	Route of Surgery	Ultrasnaging (% node detected ^a)	Tracer	injection site (o'clock)	DR	BDR	Accuracy (%)		FN
											isolated	total	
Ballester et al, 2011	P	2007-2009	111	Type 1 86%	Laparoscopy Laparotomy	Y (50%)	TC, B	3,6,9,12 (Te) 3,9 (B)	89	52.5	0	5	0
Khouiry et al, 2011	P	2005-2010	226	Type 1 80%	Robotic Laparoscopy Laparotomy	Y (25%)	B	3,9	84	67	1	5	NR
Barinnet al, 2012	P	2005-2011	498	Type 1 79%	Robotic Laparoscopy Laparotomy	Y	TC, B	3,9 small number at fundus	81	51	0.5	4	1.9
Desai et al, 2014	R	2011-2013	120	Type 1 87.5%	Robotic assisted	Y (50%)	B	3,9	86	52	0	0	0.87
Jewell et al, 2014	R	2011-2013	227	EC type I 74% CC 8% CAH 5%	Robotic assisted	NA	Overall ICG ICG+B	3,9 3,9 3,9	95 95 93	79 79 77	NR -	10 -	NR -
Fraai et al, 2015	P	2007-2009	133	Type 1 84%	laparotomy laparoscopy	NR	B+Te	3,9	86.4	52.5	0	2.63	NR
Naooura et al, 2015	R	2001-2012	180	Type 1 90%	NR	Y (41%)	Tc+B	3,9	88	63	NR	NR	6 (2.3 in low-int.gr)
Tanner et al, 2015	P	2012-2014	111	Type 1 72% CAH 16%	Robotic assisted	NR ^c	ICG, B	3,9	85.6	62.2	NR	NR	NR
How et al, 2015	P	2013-2014	100	Type 1 81%	Robotic assisted	Y (33%)	Overall ICG B TC	3,9 3,9 3,9 3,9	92 87 71 88	76 65 43 71	2 -	6 -	1 -
Hagamet al, 2016	P	2012-2015	108	Type 1 82%	Robotic assisted	Y (25%)	ICG	3,9	96	78	NR	3	NR
Paley et al, 2016	P	2012-2015	123	Type 1 82%	Robotic assisted	Y (44%)	ICG	2-3,9-10	96.7	80	NR	8	0
Simno et al, 2016	P	2012-2015	114	Type 1 68%, CAH 21%	Robotic assisted	Y (37%)	ICG	3,9	86%	62.3%	NR	NR	2
Emma et al, 2017	P	2012-2015	385	Type 1 82%	Robotic assisted	Y	ICG	3,9	86	52	<1	23	3
Lui et al, 2017	R+P	2014-2016	166	Type 1 82%	laparoscopy	Y (31%)	ICG	3,9	95.4	74.5	NR	NR	NR
Person et al, 2017	P	2014-2016	102	high risk EC	Robotic assisted	Y	ICG Reinjection ^b	2,4,6,8 3,9	96 100	88 96	0 NR	0 NR	NR NR

a: Percent of SLN detected based on ultrasnaging. b: Reinjection ICG. In case of unidentified bilateral SLN, ipsilateral injection of an additional 0.25 mL of ICG (0.625 mg) was injected. B = blue dye; BDR = bilateral detection rate; CC = cervical cancer; CAH = complex atypical hyperplasia; DR = detection rate; EC = endometrial cancer; FN = false negative rate; ICG = indocyanine green; NR = Not report; P = Prospective study; PAN = para-aortic node; R = Retrospective study; Te = Technetium

tracer and the result showed the overall detection rate of 86-97.5%, the bilateral detection rate of 65-88%, which was higher than the previous studies using Tc or blue dye (DR 70-89%, BDR 43-71%). The most common injection site of ICG was 3, 9 o'clock of the cervix at superficial (1-3 mm) and deep stromal injection. Persson *et al.*, used the reinjection technique, in case of unidentifiable bilateral SLN, ipsilateral injection (1-2 cm) of an additional 0.25 mL of ICG (0.625 mg) was injected. This method increased the detection rate to 100% and bilateral detection rate to 96% [15]. The reinjection technique could decrease the rate of side specific full lymphadenectomy if failed mapping or SLN is not identified. The false negative rate was less than 3% in low to intermediate risk of histology and 6% in high-risk histology [16]. Ultrastaging increased the detection of node metastases 25-50%.

Evaluation of aortic node

The most common anatomic sites where SLN were identified were interiliac 36%, external iliac 30%, obturator 23%, and common iliac 8% regions [17]. This review showed that the isolated para-aortic node was uncommon (1-2%) even in high-risk histology. This result was correlated with the studies of Abu-Rustum *et al.* in 2009 which found that para-aortic SLN involvement was identified in only 1.6%, respectively [12]. Para-aortic lymph nodes can be classified based on their location above and below the inferior mesenteric artery (IMA). Mayo Clinic found that the majority of para-aortic node invasion involved in the area above the IMA [18]. For surgeons who routinely perform lower aortic nodal dissection, pelvic mapping may be informative of both the pelvic and lower aortic nodal basins and may be an acceptable substitute [19] Sari *et al.*, performed para-aortic LN dissection at the level of aortic bifurcation up to the level of renal vein. They found that the presence of a lympho-vascular space invasion (LVSI) and pelvic LN involvement appear to be independent risk factors for para-aortic node metastasis [20]. Therefore, the frozen section analysis of LVSI during surgical staging may be considered.

Predictor of success: method, surgeon, patient or pathology

1) Site of injection

Cervical injection: The most common and most easily accessible way is a cervical injection. According to Memorial Sloan Kettering Cancer Center (MSKCC) algorithm, combined superficial and deep cervical injections are adequate. There are three rationales included; first, the main lymphatic drainage to the uterus is from the parametrium. Therefore, the cervical injection is preferred than uterine fundal serosa mapping which does not reflect the main route of drainage. Second, the cervix is rarely distorted by anatomic variations, such as myoma or prior procedure, such as conization or tumor infiltration in women with endometrial cancer. Lastly, the majority of early-stage endometrial cancers do not have disease infiltrating and

ulcerating the uterine fundal serosa. The result from one systematic showed the detection rate of SLN with ICG tracer were 78-100% for cervical injection and 33-100% for hysteroscopic injection [21]. There is no difference in detection rate between cervical injection at two or four quadrants (22). The main concern is the potential to miss metastatic spread to the para-aortic lymph node. Abdullah *et al.*, reported that cervical injection increased bilateral SLN detection, especially in iliac node group but decreased the rate of para-aortic detection [23]. Increasing the detection rate of para-aortic node metastases could be achieved by corporeal injection and deep cervical injection [24] Abu-Rustum *et al.*, demonstrated that addition of fundal injection to the cervical injection did not appear to produce a higher detection rate [12]. The evidence from this review (Table 1) supports cervical injection as the preferred injection site due to high detection rate and most feasible choice.

Hysteroscopic guide sub-endometrial tumor

The hysteroscopic approach focuses on a peritumoral injection. The major criticism of cervical injection is the low rates of mapping in the aortic area. To increase aortic node detection, the hysteroscopic visualized with tracer injected surrounding lesion at endometrium have been performed. Some believe that this method may represent tumor drainage better than other techniques. The initial published reported a high rate of detection in both the pelvic and para-aortic nodal areas. The detection rate with scintigraphy was 78% and with blue dye it was 63%. The sensitivity and specificity were 100% when using this method with combined blue dye and Tc. SLNs were detected at the para-aortic lymph node area by only hysteroscopic radioisotope injection (56%). [25]. Nevertheless, this method is not simple when the tumor is either too large and occupying the entire endometrial cavity, or too small and more difficult to identify. Compared with cervical injection, this method is uncomfortable, more difficult to inject, and some studies reported that the detection rate did not improve [25].

Sub-serosal uterine fundus

The detection of subserosal fundal myometrium with both blue dye and Tc was 45-61% [26]. The detection rate improved when combined subserosal with cervical injection (83.3% by combined application vs. 61.5% by serosal myometrium) [27]. Nevertheless, the detection rate of combined method did not improve compared to the result from cervical injection alone. This method was uncommonly used due to its low detection rate and not feasible when there is distortion secondary to leiomyoma.

2) Tracer

Comparing several techniques, it appears that near-infrared fluorescent imaging with ICG (NIR/ICG) has the highest detection rate of SLN in endometrial cancer [28-30]. Cibula *et al.* reported the bilateral detection rate of SLN mapping in endometrial cancer using ICG alone, blue dye alone, ICG plus blue dye, and Tc plus blue dye were 79%, 61%, 75% and 77%, respectively, thus rendering blue

dye and Tc unnecessary [10] ICG brings strong sensitivity above 83%, in most cases, and NPV of 88-100% [21]. ICG injection technique can easily be performed with high accuracy and low toxicity. One study reported 1% of women (1/93) in the form of anaphylactic reaction to methylene dye despite negative preoperative skin sensitivity test [31]. No adverse effect of ICG has been reported. The only limitation was the dependence on fluorescence imaging technology which has a high cost for initial investment. There is no consensus regarding ICG concentration and volume used. The recommended concentration was 1.25 mg/ml. It could be used 4 ml, divided into 2 ml injected at 3 and 9 o'clock with 1 ml deep and 1 ml submucosally. Holloway *et al.* used 2.5 mg of ICG with higher detection rates, and because of ICG safety and non-toxicity features, the use of doses as high as 2.5 mg could be a successful choice [32].

3) Route of surgery

In one prospective comparative trial, SLNs detection rate was significantly higher through laparoscopy than through laparotomy after dye pericervical injection (82% vs. 41%; $p = 0.008$) [33]. The different detection rates might depend on the different time interval elapsing between the injection of the vital dye into the cervix and the surgical SLNs assessment in the pelvic basin. An updated systematic review and meta-analysis found that laparoscopic surgery and robot-assisted surgery, were associated with high detection rates and sensitivities when compared with an open surgery based approach [13].

4) Surgeon's experience

Khoury-Collado *et al.* studies regarding the learning curve of SLN mapping technique determined how many SLN mapping cases a surgeon needed to perform in order to reach that 90% benchmark. The authors suggested that more than 30 cases are needed to significantly improve detection rates (improved from 77% to 94%) [34]. How *et al.* recommended that in the early stage, the surgeon should consider performing full lymphadenectomy and using a dual tracer to ensure low false negative before changing to sentinel node biopsy without comprehensive staging. The number of cases needed to achieve a certain level of proficiency depends on the individual surgeon. The surgeons need to establish their own detection rates and false negative rates to determine whether they can offer this option to their patients [34].

5) SLN number

One retrospective study of 84 patients with endometrial or cervical cancer reported that the number of SLNs removed was influenced only in cases where the operating surgeon had performed more than 20 laparoscopic ICG SLN mapping. However, the high number of SLN removed is not associated with a reduced false negative of SLN in both endometrial and cervical cancer. False negative rate in group of SLN number less than four and more than three were 4.8% and 0%, respectively [35]. The removal of all stained lymph nodes may not necessarily improve the ac-

curacy of the SLN mapping.

6) Body mass index (BMI)

The effect of BMI to successful SLN mapping showed conflicting results. Some studies reported that detection rate appeared to be influenced by BMI [36-37]. Jewell *et al.* assessed the detection rate of SLN using NIR/ICG for uterine and cervical malignancies. The heavier patients had a lower likelihood of mapping and less mapping bilaterally. It appears that patients with BMI greater than 34 are less likely to undergo bilateral SLN mapping [36] Tanner *et al.* performed SLN mapping in women with EC or complex atypical hyperplasia (CAH) via cervical injection of ICG or Blue dye followed by the robotic-assisted total laparoscopic hysterectomy. BMI was associated with successful bilateral SLN mapping rate with OR 0.95 [37]. On the other hand, the result of more recent studies, a large prospective study of 102 patients [38] and one systematic review of 4,915 women [39] reported that there is no significant difference in the overall and bilateral success rate between normal and obese patients.

7) Tumor grade, FIGO stage, or histology type

One retrospective multicentric study reported that there was no difference on overall and bilateral SLN detection rate according to ESMO risk group, the detection rate, and bilaterality were comparable in low/intermediate and high-risk groups (respectively, 88%, 88%, 64%, and 60% $p > 0.05$) while FN was higher for patient at high risk (9%) compared to the entire population (3%). This poses the question of the usefulness of the SLN procedure in this specific population. [16] Farghali *et al.* evaluated the accuracy of SLN of 93 women with EC using laparotomy approach with methylene blue injected into subserosal myometrium approach, and there was no significant relation between rate of SLN detection and tumor grade, and FIGO stage or histology type [31]. This result is in agreement with the systematic review [28], which showed no difference in the sensitivity of SLN detection by histology. Touhami *et al.* reviewed 128 patients with only high risk EC (Grade 3 endometrioid, clear cell, serous or carcinosarcoma) undergoing surgery with SLN mapping followed by pelvic lymphadenectomy. Successful SLN mapping occurred in 89.8% with a bilateral detection rate of 63.2%. A sensitivity and NPV were 95.8% and 98.2%, respectively. [40]. The latest version of NCCN guidelines revised the role of SLN mapping for EC staging that sentinel node mapping may also be used in high-risk histologies of apparent uterine confined disease [41].

Cervical cancer

Reliability of sentinel node mapping

SLN mapping is feasible and results in a high detection rates in women with early-stage cervical cancer. As shown in Table 2, the overall detection rates were almost 100% and bilateral detection were 100% and 60-70%. Diab *et al.* reported a pooled detection rate and pooled sensitivity of

Table 2. — *The accuracy of sentinel node mapping in recent studies of early stage cervical carcinoma.*

Author	No of patients	Surgery	Tracer	Diagnostic accuracy
Van der Vorst et al, 2011	9	RA-RH or Fertility sparing surgery (laparotomy)	ICG-HSA	- DR 100%
Crane et al, 2011	10	RHND (laparotomy)	ICG, B	- DR: ICG 97% Blue dye 77%
Beavis et al, 2016	30	RA-RH or Fertility sparing surgery	ICG	- DR 100% - BDR 87% - Metastatic node 16.7%
Bat AS et al, 2015	139	RH or TH (Laparoscopy)	Tc99m, B	- DR 87.8% - BDR 67%
Wuntakal et al, 2015	132	RH or TH (Laparoscopy or laparotomy)	Tc99m + blue dye	-DR 100%
Tanaka et al, 2017	119	RH or TH (Laparoscopy or laparotomy)	Tc99m, B, ICG	- DR: Tc99m 85.8%, Blue dye 20.3%, ICG 61.6%
Salvo et al, 2017	188	RH or TH (Laparoscopy or laparotomy or Robotic assisted)	B +/- ICG	- DR 90% (ICG 89%) - BDR 62% - NPV 99.3% Sensitivity 96% - Metastatic node 3.6%

B = blue dye; BDR = bilateral detection rate; DR = detection rate; ICG = Indocyanine green; ICG-HAS = ICG absorbed to human serum albumin; NPV = Tc = Technetium; TH = Trachelectomy; RH = Radical hysterectomy; RHND = radical hysterectomy with node dissection;

89.2% and 90%, respectively [42]. Most of the previous studies were of a retrospective design. One prospective multicenter SENTICOL study included 139 patients that received combined radioactivity and blue dye and reported a good detection rate of 87.8% and bilateral detection rate of 67%. Further prospective studies are needed to determine if SLN mapping can replace lymphadenectomy in this setting [43].

Location

The commonly identified SLN area was external iliac region, either just medial or lateral to the iliac bifurcation. Nearly 50-70% are located in obturator basin near the joint

of internal and external iliac veins; 10% are located in less common regions included common iliac, presacral or parametrial area and, more importantly, in 4–9% of patients, the SLN were located above the aortic bifurcation in the para-aortic region [10, 44] The advantage of SLN mapping is the identification nodes outside of routine lymphadenectomy areas, providing additional histological information which improves staging. The location of the sentinel node in early-stage cervical carcinoma is presented in Table 3.

Predictor of success: method, surgeon, patient, or pathology

1) Age and BMI

Table 3. — The location of sentinel node in early stage cervical carcinoma.

AUTHOR	IDENTIFIED SITE						
	Internal iliac node	Obturator node	External iliac node	Common iliac node	Parametrium Pelvic NOS	Pre-sacral	Para-aortic node
Bat AS, 2015 (intraoperative)	80.29%			8.11%	7.16%	1.19%	3.58%
Wuntakal et al, 2015	23.6%	25.3%	38.6%	-	-	1.4%	0.7%
Beavis et al,2016	40.3%	26%	20.8%	-	-	-	-
Salvo et al, 2017	41.9%		31.6%	10%	13.3%	0.8%	2.4%

NOS = non-otherwise specified

Wuntakul *et al.* assessed the factors affecting bilateral SLN detection, using gamma probe and blue dye, Old age and elevated BMI were significantly associated with lower SLN count with preoperative SPECT/CT (age: $p = 0.005$, BMI: $p = 0.01$) and gamma probe (age: $p = 0.005$, BMI: $p = 0.02$) but only elevated BMI was associated with lower SLN count by blue dye ($p = 0.008$). Unilateral detection rate independently associated with older age may be due to sclerosis in lymphatic vessel or decrease perfusion in elderly [45]. The result of the association between older age and detection rate was similar to other studies. From SENTICOL study, age was an independent factor associated with both overall detection rate (OR 0.91, 95% CI 0.87–0.96) and bilateral detection (OR 0.95, 95% CI 0.92–0.98) [43]. Tanaka *et al.* also reported that elder patients (≥ 60 years) had lower detection rate than younger patient (< 60 years) (65.8% vs. 85%, $p < 0.01$). In older patient, the sensitivity was decreased and FN rate was increased but did not differ to a statistically significantly (sensitivity, 57% vs. 57% $p = 0.3$, FN, 14.3% vs. 4.1% $p = 0.1$). All of detection rate, sensitive, and FN did not differ among severely obese, moderate obese, or non-obese. (DR, 93.8% vs. 80.4% vs. 81.2%, $p = 0.2$, $p = 0.9$; sensitivity, 75% vs. 50% vs. 72.0%, $p = 0.9$, $p = 0.5$; FN, 8.3% vs. 3.6% vs. 5.5%, $p = 0.7$, $p = 0.7$, respectively. Not only BMI, this study also found that parity, histology type, and history of conization also had no impact on the detection rate, sensitivity or FN rate [46].

2) Neoadjuvant chemotherapy

The detection of SLN mapping in patients who received neoadjuvant chemotherapy was lower than those were not receive significantly (67.9 vs. 86.3%, $p < 0.01$) [46]. Previously, published study of laparoscopic SLN procedure with gamma probe and patent blue dye also noted that false negative rate increased to 33.3% in patient with neoadjuvant treatment vs. 7.7% in patients without this treatment.

Bilateral detection was also lower in subgroup [47].

3) History of conization

The injection of tracers to patients with a history of conization is difficult and conization may hamper lymphatic flow. Coutant *et al.* showed that overall detection and bilateral detection rates were higher in the subgroup patients who did not have preoperative conization, but it was not statistically significant because of the small number of patients. The false negative rates compared with the patients without preoperative conization were 33.5% and 8.3%, respectively [47]. The authors explained that the lymphatic drainage could be modified, and the dye could have been injected too deep in the intraperitoneal area in the remaining part of the cervix. However, Wuntakul *et al.* and Salva *et al.* found that previous conization did not seem to influence the detection of SLN [45, 48].

4) Tumor size

Some authors concluded that tumor size is not associated with the overall and bilateral detection rate of SLN in early-stage cervical cancer [48, 49]. However, most of the studies found that the ability to detect bilateral sentinel nodes was limited by tumor size. These authors did not recommend SLN mapping in tumor size 2 cm or more [46, 50–52]. The larger volumetric tumor may disturb lymphatic channel drainage and the centrally necrotic part of the tumor may cause a retrograde leakage of dye [51]. One meta-analysis confirmed these findings with a detection rate, sensitivity, and NPV of 94.5%, 100%, and 100%, respectively, in tumors < 2 cm compared to 80.1%, 89.3%, and 94.9% for larger tumors [53]. In advanced stage cervical cancer, NPV of SLN is lower and frozen section is not sufficiently reliable, thus is not yet felt to be reliable for clinical practice [28].

5) Laparoscopy and mapping agent

A wide and clear view by laparoscopy may improve detection rate. Tanaka *et al.* reported that laparoscopy had

Table 4. — The location and accuracy of sentinel node mapping of ovarian carcinoma.

Author	No case (total /EOC)	Surgery	Tracer and time of injection	Site of injection	SLN location					Diagnostic accuracy		Node positive
					Para-aortic node			Pelvic	Pelvic + PAN	Overall DR	NPV	
					above IMA	around IMA	below IMA					
Negishi et al, 2004	11 (11)	laparotomy	CH40 10 min before start node dissection	Ovarian cortex	91%	36%	36%			100%	100%	
Nyberg et al, 2011	16 (14)	laparotomy	Te-99m +blue dye 10-21 min before operation	Near hilum of the ovary	33%	-	67%			94%		
Kleppe et al, 2015	21 (5)	laparotomy	Te-99m +blue dye	Uterovarian and IP ligament	67%			9%	24%	96%		
Buda et al, 2016	10 (6)	laparoscopy	ICG	Uterovarian and IP ligament	27%	53%	-	20%		90%	100%	
Hassanzadeh et al, 2016	35 (11)	laparotomy	Te-99m (+blue dye in some case) before remove mass	Ovarian cortex (10), Uterovarian and IP ligament (25)	85%			8%	8%	71% Cortical group 40% Subperitoneal group 84%	100%	12%
Nyberg et al, 2017	20 (3)	laparotomy	Te-99m + blue dye at the beginning of operation	Uterovarian and IP ligament	60%			10%	30%	100%	100%	33%

CH40 = carbon particle; EOC = epithelium ovarian cancer; DR = detection rate; ICG = Indocyanine green; IMA = Inferior mesenteric artery; NPV = negative predictive value; PAN = para-aortic node; Tc = technetium

higher detection rate than laparotomy (100% vs. 77%, $p = 0.01$) [46]. Salvo *et al.* found no difference in detection rate among laparotomy, laparoscopy, and robotic surgeries [48]. Feijoo *et al.* performed SLN mapping with RHND by laparoscopy and laparotomy, they founded that the overall detection rates of both groups were 100%. There were no differences in overall and disease-free survivals [54].

6) Tracer

NIR fluorescence imaging with ICG is an excellent and safe tracer modality for SLN mapping with a 96% overall and 88% bilateral detection rate. These results were higher when compared with blue dye and ICG has also been established as accurate, safe, and reproducible in patients with cervical cancer [42]. Preclinical work has demonstrated that adsorption of ICG to human serum albumin (HSA, a complex is ICG: HSA), by simply mixing it, increases the fluorescence intensity and hydrodynamic diameter [55]. One double-blind, randomized trial showed no advantage of ICG-HAS over ICG alone for the SLN procedure in early-stage cervical cancer [56]. Further optimization is required to improve the intraoperative detection rate., although there is no randomized control trial that has been published and no conclusion about the most effective surgical route and tracer agent. Most of the recent studies to date using the robotic or laparoscopic platform with ICG and NIR fluorescence technique showed satisfactory diagnostic accuracy. Compared to radiocolloid technique, this technique does not require preoperative injection and gives a higher satisfaction score [57].

Ovarian cancer

Surgical staging is critical to tailor the appropriate chemotherapy in women with early-stage ovarian cancer. Systemic pelvic and para-aortic lymphadenectomy could be avoided if thoroughly investigated that sentinel nodes

could predict whether residual nodes will be involved or free of disease. There is limited data regarding the SLN mapping in ovary. The problems of this approach are the risk of tumor dissemination and inconvenient injection site, especially when bulky ovarian masses are present. According to lymphatic drainage pathways of the ovary, there are two major routes for drainage: 1) drainage via the suspensory or infundibulo-pelvic ligament to paracaval and para-aortic node, and 2) via proper ligament to the obturator fossa and internal iliac node [58]. For this reason, the most common injection site of previous studies was sub-peritoneum of the suspensory and utero-ovarian ligaments. Other injection sites reported in literature were sub-cortical and trans-cervical injections into the fundal and midcorpal myometrium [59-61]. Table 4 shows the studies of SLN mapping in ovarian tumor, the number of cases performed including SLNB are much lower than studies of cervical and endometrial cancer.

The acceptance of laparoscopy for surgical staging women with ovarian cancer is still limited. Therefore, laparotomy approach with using combined radiocolloid and blue dye is the most common technique. Only one study performed laparoscopy with ICG technique. The common site of detected SLN was located at para-aortic area. The data of diagnostic accuracy, although limited, provided results with almost 100% of overall detection rate and 100% of NPV. This result revealed that SLN mapping seems feasible and promising. Further investigations are necessary to evaluated the possibility to implement this concept in ovarian cancer.

Conclusion

Results from well-designed studies supported using sentinel lymph node mapping could replace the full lymphadenectomy in early stage vulvar, endometrial, and

cervical cancer. Limited studies also provide promising results in early ovarian cancer. This procedure does not only decrease the morbidity from surgery, it might improve diagnostic accuracy by ultrastaging or detection lymph node outside routine lymphadenectomy. However, the gynecologic oncologists should consider the limitations or the issues which have not yet been proven, such as some factors associated with accuracy of procedure, role of ultrastaging, and adjuvant therapy, including the impact on the patient outcome.

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