

Review

A short review of current implementations of sentinel lymph node mapping in gynecologic cancers

Altın et al. Sentinel lymph node mapping in gynecologic cancers

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Abstract

Lymph node metastasis both upstages the disease and alters adjuvant treatment plans in gynecologic cancers. Since minority of the patients have nodal metastasis, many patients unnecessarily undergo complete lymphadenectomy and face its morbidities. Sentinel lymph node (SLN) mapping is an alternative for evaluation of lymph nodes with lesser side effects. Although it is yet an experimental approach in ovarian cancer, it has been incorporated into guidelines for endometrial, cervical and vulvar cancers. We aimed to summarize the current situation of SLN mapping in gynecologic cancers.

Keywords: Sentinel lymph node, endometrial cancer, cervical cancer, vulvar cancer, ovarian cancer

Introduction

Lymphadenectomy is part of surgical staging in gynecologic cancers. since it is important to determine the nodal status for guiding the adjuvant treatment. But only minority of the cases have nodal metastasis and many patients face morbidities associated with complete lymphadenectomy unnecessarily. Sentinel lymph node (SLN) mapping has been proposed as a less invasive technique used for assessment of lymph nodes in gynecologic cancers. The lymph node that has direct connection to the tumor site, and most likely to receive first metastasis is called as sentinel lymph node (SLN). Therefore, with SLN mapping while nodal

metastasis is identified, morbidities of complete lymphadenectomy can be avoided in node negative patients.

SLN mapping has gained importance in staging of gynecologic cancers in the last decade and it has been incorporated into National Comprehensive Cancer Network (NCCN) Guidelines for endometrial, cervical and vulvar carcinomas (1-3). But it is yet an experimental approach for ovarian carcinoma.

Technetium-99m (99mTc), indocyanine green (ICG) and blue dyes can be used alone or combined for identifying SLNs. All suspicious lymph nodes must be removed besides SLNs and side-specific lymphadenectomy should be performed in case of mapping failure.

SLN mapping allows detection of uncommon drainage sites such as internal iliac lymph nodes that may not otherwise have been resected. Another advantage of SLN mapping is detection of more nodal metastasis by pathologic ultrastaging which cannot be identified by routine hematoxylin and eosin (H&E) staining. To do so, SLNs are cut at 50-200 μm intervals and two paraffin embedded slides are prepared at each section. One slide is stained with H&E and the other with immunohistochemistry stains (AE1 and AE3 anticytokeratin antibodies) if no metastasis is identified by H&E examination. Tumor deposits >2 mm are defined as macrometastasis. Micrometastasis is defined as metastatic deposits ranging from 0.2 mm to no more than 2 mm and isolated tumor cells (ITCs) are defined as single tumor cells or clusters <0.2 mm.

Although it has been shown that SLN algorithm is a highly sensitive method and has high detection rate and negative predictive value (NPV), survival data comparing only SLN removal and complete lymphadenectomy is insufficient (4-6).

SLN mapping allows detection of uncommon drainage sites such as internal iliac lymph nodes that may not otherwise have been resected. Another advantage of SLN mapping is detection of micrometastasis and isolated tumor cells (ITCs) by pathologic ultrastaging which cannot be identified by routine hematoxylin and eosin (H&E) staining.

This review aims to summarize current SLN mapping implementations in gynecologic cancers.

Endometrial cancer

Endometrial cancer is surgically staged which includes hysterectomy with or without oophorectomy and lymphadenectomy. Nodal status not only changes the stage of the disease but also guides the adjuvant treatment plans. However, most of the endometrial cancer patients are diagnosed in early-stage when the disease is limited to uterus and many patients undergoing complete lymphadenectomy face intraoperative and postoperative complications (eg. neurovascular injuries, lymphedema and lymphocele formation) unnecessarily (7, 8). Moreover, two randomized studies showed that lymphadenectomy does not provide survival advantage in early-stage patients (9, 10). Therefore, approach to lymph node evaluation is an issue of debate.

Many centers perform selective lymphadenectomy as the uterus is sent to intraoperative frozen section evaluation and no further lymphadenectomy is performed when the analysis reveals grade 1 or 2 tumors invading less than 50% of the myometrium and smaller than 2 cm (11). These criteria are also known as Mayo criteria and the risk of nodal metastasis in this low-risk population is less than 5% (11, 12). However, only 20% of high-risk patients have nodal metastasis and many patients still undergo unnecessary lymphadenectomies (13). Moreover, accuracy of frozen section is higher in more experienced centers and not all centers may have a frozen section unit to guide the surgery (14, 15).

SLN mapping algorithm is a less invasive technique for evaluation of nodal status. Both in prospective and retrospective studies, sensitivity and NPV of SLN mapping algorithm were reported between 84-97% and 97-99%, respectively (4, 16-19). It has been shown that SLN algorithm does not compromise overall detection of stage IIIC disease both in low-risk and

high-risk endometrial cancer patients (20, 21). In a meta-analysis including 55 studies, bilateral and overall detection rate of SLN mapping were 50% and 81%, respectively (4). With these promising data, SLN mapping algorithm is also incorporated into NCCN guidelines despite lack of randomized studies comparing survival outcomes of SLN mapping and complete lymphadenectomy (1).

Technetium-99m (99mTc), blue dyes (1% methylene blue, 1% isosulfan blue or 2.5% patent blue sodium) or indocyanine green (ICG) can be used for lymphatic mapping. ICG requires near-infrared camera for visualization, but it is shown to be superior to blue dye alone and equal to combination of 99mTc and blue dye in terms of SLN detection (22). Whichever dye is used, 1 mL deep (1 cm) and 1 mL superficial (3-4 mm) cervical injections are done at 3 and 9 o'clock positions before hysterectomy. Although fundal or hysteroscopic injections lead to higher mapping in paraaortic area, they do not provide higher detection rates in pelvic area compared to cervical injection (23). Optimal detection of SLNs occurs 15-60 minutes after the injection. All identified SLNs and any enlarged or suspicious lymph nodes should be removed. Side-specific lymphadenectomy is required if a hemipelvis does not map. Paraaortic lymphadenectomy is not an essential step of SLN algorithm and done at surgeon's discretion (Figure 1).

Comparing to complete lymphadenectomy, although fewer nodes are removed, 4.5-8% additional lymphatic metastasis is detected with SLN algorithm as a result of ultrastaging (18, 24). SLNs are cut at 50-200 μ m intervals and two paraffin embedded slides are prepared at each section. One slide is stained with H&E and the other with immunohistochemistry stains (AE1 and AE3 anticytokeratin antibodies) if no metastasis is identified by H&E examination. Tumor deposits >2 mm are defined as macrometastasis. Micrometastasis is defined as metastatic deposits ranging from 0.2 mm to no more than 2 mm and ITCs are defined as single tumor cells or clusters <0.2 mm. One step nucleic acid amplification assay (OSNA) is a new method for intraoperative SLN assessment which detects cytokeratin 19 messenger RNA in metastatic lymph nodes. Compared to classic ultrastaging, more nodal metastasis is detected by OSNA, but no nodal tissue is left for postoperative assessment. Though, prognostic significance of these metastases detected by OSNA is not known (25, 26). Currently, micrometastasis is regarded as node positive and managed accordingly, but prognostic significance of ITCs is unknown and adjuvant treatment of patients with ITCs is given according to primary tumor characteristics (25, 27). Yet, more studies are needed to clarify the clinical relevance and treatment of patients with ITCs.

In some retrospective series, it has been shown that removal of only SLNs does not have a negative effect on oncological outcomes both in low- and high-risk pathologies as 3-year overall survival (OS) and disease-free survival (DFS) were comparable between SLN algorithm group and lymphadenectomy groups (21, 26-29, 28-31).

Cervical cancer

Lymphatic metastasis has negative effect on prognosis and alters treatment plans in cervical cancer. Sensitivity of preoperative imaging studies for nodal metastasis is reported below 75% and surgical evaluation is generally needed (30, 32). The risk of nodal involvement is <1% in stage IA1 cervical cancer and there is no need for lymphadenectomy in this stage when there is no lymphovascular space invasion (LVSI). But for stage IA2 and beyond diseases, at least SLN removal is needed.

SLN biopsy in cervical cancer appears promising. Cervical injections are done with ICG, blue dye or 99mTc at 2 or 4 points (2). All enlarged and suspicious nodes must be removed besides SLNs. Side-specific lymphadenectomy is mandatory if SLN is not detected. One hundred and thirty-nine women with stage IA1 to IB2 cervical cancer were recruited to SENTICOL study, at least 1 SLN was detected in 98% of the patients, and sensitivity and NPV were 92% and 98.2%, respectively (31, 33). In another study, SLN detection rate, sensitivity and NPV were

88.6%, 77.4% and 94.3%, respectively (3234). Although SLN technique can be used in tumors up to 4 cm, best detection rates, sensitivity and NPV are achieved in tumors smaller than 2 cm (5, 3234). Moreover, studies have demonstrated that SLN biopsy is completely reliable if bilateral SLNs are detected (31, 33, 35).

Similar to endometrial cancer, ultrastaging is performed if no metastasis is identified in SLN with routine H&E staining. A recent study showed that patients with micrometastasis and ITCs had similar DFS compared to node negative patients (92.7% vs 93.6%) and DFS did not improve with adjuvant treatment in these patients (3436). Yet more studies are needed to clarify clinical significance and treatment of low-volume metastasis. The ongoing prospective randomized SENTICOL III and SENTIX studies aim to find out whether DFS, recurrence rate and quality of life differs between patients with cervical cancer undergoing only SLN biopsy and completion bilateral pelvic lymphadenectomy after SLN biopsy.

Vulvar cancer

Lymphatic metastasis is the most important prognostic feature in vulvar cancer and the 5-year disease specific survival for node positive and negative patients were reported between 70-93% and 25-41%, respectively (3537). Primary tumor should be resected with at least 1 cm clear margins and either unilateral or bilateral inguofemoral lymph nodes or in selected patients SLNs should be removed. There is no need for inguofemoral lymphadenectomy for stage IA patients since risk for nodal involvement is <1% (3638). But patients with stage IB or higher stages have $\geq 8\%$ risk of nodal metastasis and lymphadenectomy is mandatory (3739). Unilateral lymphadenectomy can be performed in case of clinically negative lymph nodes when the tumor is <4 cm and ≥ 2 cm lateral to vulvar midline (3).

20-70% of the patients experience surgical morbidities such as wound breakdown and lymphedema due to inguofemoral lymphadenectomy (3840). SLN biopsy is an option for inguofemoral lymphadenectomy in selected early-stage patients whose tumors are unifocal and smaller than 4 cm and in whom imaging and/or clinical examination reveals negative lymph nodes (39, 4041, 42). For tumors >4 cm, SLN technique is both associated with reduced sensitivity and higher groin recurrences (4143). It is also recommended completion of inguofemoral lymphadenectomy after SLN biopsy in at least 10 cases before performing SLN biopsy alone. Best SLN detection rates are observed when ^{99m}Tc and blue dye are used together (40, 42, 44).

^{99m}Tc is injected 2-4 hours prior to the operation and a gamma probe is used to detect the SLN. The most commonly used blue dye is isosulfan blue 1%. 4 cc blue dye is injected intradermally into the normal tissue around the tumor at 2, 5, 7 and 10 o'clock positions. It is recommended to perform SLN biopsy prior to excision of vulvar tumor so lymphatic network will not be disturbed. Side-specific inguofemoral lymphadenectomy is recommended when SLN is not detected.

In GOG-173 study, SLN biopsy was prospectively compared to inguofemoral lymphadenectomy in 452 patients with squamous cell carcinoma with tumors ranging 2-6 cm and at least 1 mm depth of stromal invasion (4042). At least 1 SLN was identified in 92% of the cases, sensitivity and NPV were 91.7% and 96%, respectively. In another prospective study, the GROINSS-V I study, investigating clinical safety and utility of SLN biopsy in early-stage vulvar cancer, false negative rate of SLN biopsy was found to be 3% (4244). Four hundred three women with stage I-II squamous cell tumors <4 cm were enrolled to this study, and no further lymphadenectomy is performed if SLNs were negative. In a study evaluating oncologic outcomes of the GROINSS-V I study participants, groin recurrence rates for SLN negative and positive patients at 5 years were 2.5% and 8%, respectively (4345).

The ongoing GROINSS-V II study is a prospective study which aims to find out whether complete inguofemoral lymphadenectomy can be replaced by adjuvant RT in patients with metastatic SLNs undergoing only SLN biopsy. Preliminary results of this study showed that

inguinofemoral lymphadenectomy can be replaced by RT safely in patients with low-volume metastasis, but not for patients with macrometastasis (4446). Therefore, when SLN metastases are >2 mm, it is recommended to perform complete ipsilateral lymphadenectomy. In such cases, contralateral lymph nodes should also be resected or treated with external beam radiation therapy (EBRT). Frozen section of SLNs may be used to for deciding to complete lymphadenectomy.

The aim of GROINSS-V III will be to examine the effectiveness and safety of chemoradiation in patients with macrometastatic SLNs.

Ovarian cancer

In ovarian cancer patients who are apparently early stage, bilateral pelvic and paraaortic lymphadenectomy is indicated to detect occult lymphatic metastasis since 1/3 of these patients have nodal metastasis and these metastases can be seen in bilateral pelvic or paraaortic nodes (45, 4647, 48). It has been shown that early-stage ovarian cancer patients who had undergone systematic lymphadenectomy had better survival outcomes compared to no lymphadenectomy (4749).

SLN biopsy is investigational in ovarian cancer. 99mTC, blue dye or ICG can be used as tracers alone or in combination (4850). Whichever dye is used, best detection rates were reported with injections on the utero-ovarian and infundibulopelvic (IP) ligaments, or only on the IP ligament if hysterectomy had been performed before, just underneath the peritoneum. Mesovarium, ovarian hilum and ovarian cortex are alternative injection sites, but lower detection rates were reported, and the latter technique may result in tumor rupture.

In a systematic review including 145 patients, overall SLN detection rate was found to be 90.3% (range 40-100%) (4850). While ICG alone resulted in 93.3% detection rate, with ICG + 99mTC combination it was 100%. Mean detection rate in the pelvic and paraaortic region were 44% (range 25-87.5%), 82% (range 70-91%), respectively. In a recent prospective cohort study including 20 patients, first unilateral salpingo-oophorectomy is performed and SLN mapping was performed with 99mTC plus 0.5 ml of ICG afterwards, if the frozen section revealed malignancy (4951). Hence, injections were done into both utero-ovarian and IP ligament stumps or only into IP ligament stump according to previous hysterectomy status. SLNs were identified in all patients in paraaortic region and in 93% of the patients in pelvic regions. The ongoing prospective SELLY trial is a phase II trial whose aim is to evaluate accuracy of SLN biopsy in diagnosing nodal metastasis in early-stage ovarian cancer patients using ICG. The preliminary results of this study including 31 patients revealed overall detection rate of 67.7% and detection rate was significantly higher in patients undergoing immediate staging surgery compared to delayed surgery. All 4 patients with lymphatic metastasis had metastatic SLNs, yielding 100% sensitivity and 100% NPV (5052).

Conclusion

Table 1 summarizes NCCN and European Society of Gynaecological Oncology (ESGO) recommendations for SLN mapping in gynecologic cancers.

Endometrial cancer

SLN mapping is an alternative method for lymph node assessment in staging of apparently early-stage low-risk endometrial cancer patients when no metastasis is detected by imaging modalities or intraoperative exploration. Recent studies showed that SLN mapping can also be considered in high-risk histologies (type 2 endometrial cancer). To date, patients with macrometastasis and micrometastasis are treated in the same way, but adjuvant treatment of patients with ITCs is given according to primary tumor characteristics. Current data showed that removal of only SLNs does not have a negative effect on oncological outcomes compared to complete lymphadenectomy, but more data are needed.

Cervical cancer

Both prospective and retrospective series have demonstrated that SLN mapping have high NPV in cervical cancer. But SLN biopsy is completely reliable if bilateral SLNs are detected. SLN mapping may be used in tumors up to 4 cm, but best detection rates are observed in tumors <2 cm.

Vulvar cancer

SLN biopsy is an option for inguinofemoral lymph node dissection in selected early-stage patients with unifocal tumors <4 cm and in whom imaging and/or clinical examination reveals negative lymph nodes. Both prospective and retrospective series have demonstrated that SLN mapping have high NPV in vulvar cancer. For tumors >4 cm, SLN technique is both associated with reduced sensitivity and higher groin recurrences.

Ovarian cancer

SLN biopsy is an investigational approach in ovarian cancer. Best detection rates were observed with injections on the utero-ovarian and IP ligaments, or only on the IP ligament if hysterectomy had been performed before, just underneath the peritoneum. Pilot studies with limited number of patients showed moderate detection rate of SLNs in pelvic region and high detection rate in paraaortic region.

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Table 1. NCCN and ESGO recommendations for SLN mapping in gynecologic cancers		
	NCCN	ESGO
Endometrial Cancer	<ul style="list-style-type: none"> - SLN mapping can be considered for apparently uterine-confined disease when there is no metastasis demonstrated by imaging studies or at exploration - SLN mapping may also be used in high-risk histologies 	<ul style="list-style-type: none"> - SLN mapping is still experimental for apparently uterine-confined disease and systematic lymphadenectomy is recommended
Cervical Cancer	<ul style="list-style-type: none"> - SLN mapping can be considered in stage IA1 with LVSI, IA2, IB1 and select IB2 cases - SLN mapping can be used in tumors up to 4 cm, but best detection rates are achieved in tumors <2 cm. 	<ul style="list-style-type: none"> - SLN biopsy is an acceptable method of LN staging for stage IA1 patients with LVSI and IA2 - SLN biopsy in addition to BPLND is strongly recommended for stage IB1-IIA1 patients. - Intraoperative assessment of SLNs is also recommended for stage IB1-IIA1 patients.
Vulvar Cancer	<ul style="list-style-type: none"> - SLN biopsy is an alternative standard of care approach to inguinofemoral lymphadenectomy in select cases - SLN biopsy can be used in patients with negative clinical examination or imaging and unifocal tumors <4 cm. 	<ul style="list-style-type: none"> - (At least) unilateral SLN biopsy for tumors >1 cm from the midline and bilateral SLN biopsy for tumors within 1 cm of the midline should be performed for unifocal T1, <4 cm tumors in case of no suspicious nodes preoperatively, and IFL should be performed if SLN is not detected or positive.
Ovarian Cancer	- Experimental	- Experimental
<p>NCCN: National Comprehensive Cancer Network, ESGO: European Society of Gynaecological Oncology, SLN: sentinel lymph node, LN: lymph node, BPLND: bilateral pelvic lymphadenectomy, IFL: inguinofemoral lymphadenectomy</p>		

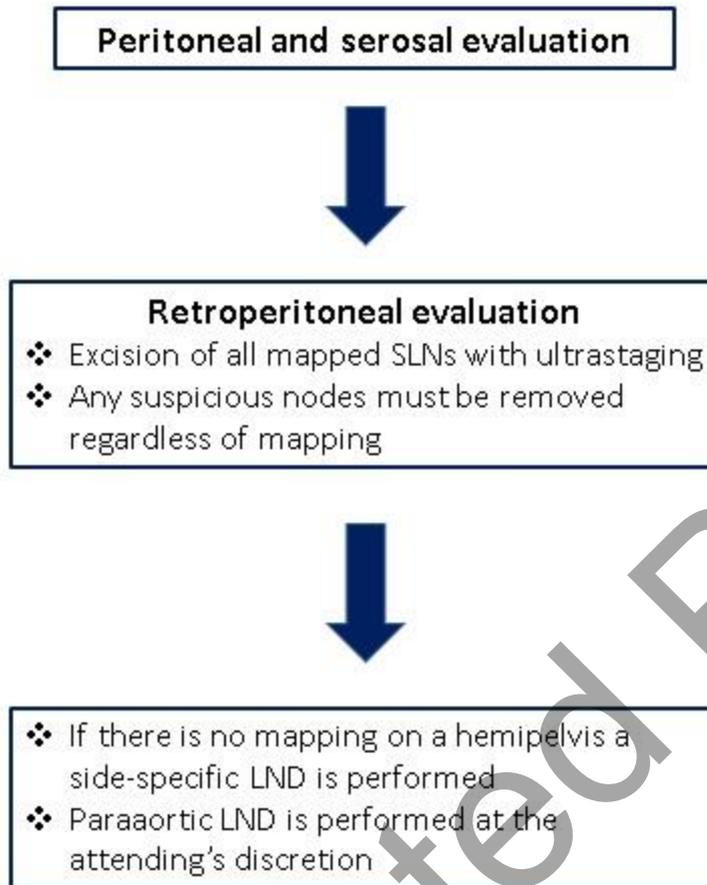


Figure 1. SLN Mapping Algorithm in Endometrial Cancer
SLN: Sentinel lymph node, LND: lymph node dissection