Role of sentinel lymph node biopsy for gynecologic cancers

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Purpose of review
To provide an overview of the current knowledge and recent advances of sentinel lymph node (SLN) assessment in uterine, cervical, vulvar, and ovarian cancers.

Recent findings
In endometrial cancer, SLN evaluation has become increasingly utilized as part of the treatment of early-stage disease, with data showing improved detection of pelvic lymph node metastasis. In cervical cancer, SLN biopsy has also gained increasing traction with studies demonstrating the feasibility and accuracy of SLN detection. Evaluation with frozen section, however, remains limited in the detection of metastases. The prognostic significance of positive SLN in vulvar cancer is currently being investigated, with preliminary data showing lower recurrence rates in patients receiving adjuvant radiation.

Summary
SLN evaluation remains standard of care to detect lymph node metastasis in early-staged endometrial cancer. In cervical cancer, SLN biopsy has been shown to be reliable, while decreasing morbidity without impacting disease-free survival in select patients. The technique and high sensitivity of SLN biopsy in vulvar cancer has been demonstrated in large prospective trials. There are no randomized controlled trials in ovarian cancer that evaluate the role of SLN biopsy on treatment and outcome; current SLN evaluation remains investigational.

Keywords
cervical cancer, endometrial cancer, ovarian cancer, sentinel lymph node, vulvar cancer

INTRODUCTION

The term sentinel lymph node (SLN) was first coined in 1960 by Gould *et al.* [1] during the study of parotid gland carcinoma. In 1992, the first application of SLN biopsy was described in early-stage melanoma, and has been widely accepted as a component of the surgical practice of that and breast cancer [2]. Since then, the concept of SLN detection and biopsy has been expanded to gynecologic malignancies [3]. SLN biopsy has been shown to reduce surgical radicality, decrease surgical morbidity, and improve the detection of lymph node metastases, particularly low-volume disease [micrometastases measuring 0.2–2 mm and isolated tumor cells (ITC) with implants <0.2 mm]. In this review, we present an overview of the current knowledge and recent advances of SLN in uterine, cervical, vulvar, and ovarian cancers.

ENDOMETRIAL CANCER

Surgery is the mainstay of therapy for endometrial cancer [4]. The role of surgical lymph node assessment remains unresolved as two prospective randomized controlled trials (RCT) failed to prove that routine lymph node dissection (LND) in clinically early-stage disease was beneficial [5,6]. SLN injection and biopsy has been proposed as a replacement for systematic LND in early-stage endometrial cancer [7]. SENTI-ENDO was a retrospective study of stage I–II endometrial cancer patients using technetium-99 and patent blue injections [8]. Detection of SLN had a negative predictive value (NPV) of 97% and a sensitivity of 84% for metastatic disease. Long-term data after 50 months of median follow-up revealed no difference in

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Curr Opin Obstet Gynecol 2022, 34:15–19
DOI:10.1097/GCO.0000000000000766

KEY POINTS

- In endometrial cancer, SLN evaluation has become increasingly utilized as part of the treatment of early-stage disease.
- In cervical cancer, studies demonstrate feasibility and accuracy of SLN detection, with comparable recurrence-free and overall survival rates between negative SLN and pelvic lymphadenectomy.
- The role of adjuvant therapy with positive SLN in vulvar cancer is currently being investigated, with recent data showing lower recurrence rates in patients receiving adjuvant radiation.
- SLN evaluation in ovarian cancer remains investigational.

recurrence-free survival (RFS) between patients with and without SLN detection [9]. The FIRES trial was a prospective, multicenter, cohort study evaluating SLN biopsy in stage I endometrial cancer undergoing LND utilizing intracervical indocyanine green (ICG) injection and SLN ultrastaging [10]. Eighty-six percent of patients had at least one SLN detected with a sensitivity of 97.2% and NPV of 99.6%. The SHREC trial aimed to determine the diagnostic accuracy of SLN in patients with high-risk apparently early-stage endometrial cancer undergoing robotic surgery [11]. SLN were identified using ICG and analyzed using ultrastaging. The bilateral mapping rate was 95% with a sensitivity and NPV of 100%. These and other studies demonstrated that SLN injection and biopsy improved the detection rates of positive lymph nodes principally through the detection of low-volume metastatic disease with ultrastaging [12]. It appears that SLN detection rates do not differ significantly between the different tracers and sites of injection with most authors favoring ICG and cervical injections [13]. However, the prognostic significance and therapeutic implications of micrometastases, and more importantly ITC, remains unclear [14]. No randomized controlled trials have been completed comparing SLN injection and biopsy to lymphadenectomy or no lymphadenectomy making inferences regarding its safety and noninferiority difficult. Still the collected data from observational trials suggests a lower risk of short-term and long-term morbidity associated with the technique along with comparable long-term oncologic outcome when compared with LND [15,16]. Another remaining question is that of the surgical management of patients with positive SLNs and the role of completion LND and intraoperative assessment in the management of these patients [17]. Intraoperative assessment or frozen section examination (FSE) can confirm resection of lymph node tissue and allow for intra-operative management decisions, potentially avoiding secondary surgeries at the price of missing small volume metastatic disease [18].

CERVICAL CANCER

Like endometrial cancer, the practice of SLN mapping for the surgical management of early-stage cervical cancer (typically described as having tumors <4 cm in size with no evidence of metastatic disease on imaging) has increased in recent years. In the prospective, multicenter SENTICOL study, Lecuru *et al.* [19] enrolled 145 women with stage IA1 with lymphovascular space invasion to stage IB1 to receive technitium-99 and patent blue for SLN detection and biopsy. Approximately 98% had at least one SLN detected, with 92% sensitivity and 98.2% NPV for lymph node metastasis detection. If bilateral SLN were detected, there was a 0% false-negative rate [19]. Injection with ICG has been shown to potentially be a superior tracer for SLN detection. In the FILM study, women with stage I cervical or endometrial cancer undergoing definitive surgical management were randomized to receive ICG, isosulfan blue, or ICG followed by isosulfan blue. ICG detected at least one node in 96% and bilateral detection was 77 vs. 74% and 32% with isosulfan blue, respectively ($P < 0.0001$). The authors reported that there were not significantly more SLN detected with the addition of isosulfan blue [20]. In SENTICOL II, Favre *et al.* [21▪▪] randomized patients with early-stage cervical cancer to SLN biopsy alone or SLN biopsy followed by pelvic lymphadenectomy if the frozen section analysis of the SLN was negative. The 4-year RFS and overall survival rates for SLN biopsy alone and SLN biopsy followed by pelvic lymphadenectomy were 89.5 vs. 93.1% ($P = 0.53$) and 95.2 vs. 96% ($P = 0.97$), respectively. Early and late morbidity was significantly reduced in the SLN alone arm including postoperative neurological symptoms and lymphedema [22]. As with endometrial cancer, SLN ultrastaging allows detection of more metastatic disease in the lymph nodes chiefly through the detection of low-volume disease. Though micrometastases may be associated with decreased survival, the significance and therapeutic implications of these findings are still not completely resolved [20].

The decision to proceed with surgery to remove early-stage cervical cancer is driven by the presence of metastatic disease in the lymph nodes. Intraoperative pathological evaluation of SLN allows the

surgeon to confirm lymph node tissue removal and to make surgical management decisions in one step. The accurate detection of SLN metastases with FSE may be limited. The SENTIX and pooled analysis of the SENTICOL I and II studies showed that the sensitivity of FSE did not exceed 56% when compared with ultrastaging even when ITC were excluded [23▪]. This, however, may be dependent on the sectioning protocols used as serial sectioning perpendicular to the long axis of SLN yields significantly higher sensitivity than sectioning along the long axis [24].

VULVAR CANCER

Inguinofemoral LND has been the mainstay of therapy for patients with stage IB and II disease without any suspicious or palpable lymphadenopathy but is associated with up to a 40% risk of wound complication and 70% risk of lower extremity lymphedema [25]. SLN has been proposed for early-stage vulvar cancer greater than 1 mm invasion without suspicious nodes in order to decrease the morbidity associated with LND and help identify the lymphatic drainage of laterally ambiguous tumors [26]. The GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I was a prospective study in which 403 women with stage I or II (tumor size <4 cm) vulvar squamous cell carcinoma had SLN biopsy with a combination of technetium-99 and blue dye [27]. If SLN biopsy was negative, no lymph node surgery was performed. If the SLN was positive or none were identified, inguinofemoral lymphadenectomy was performed. A long-term update of the trial showed a groin recurrence rate of 2.5% for SLN-negative patients at 5 years, with a 10-year disease-specific survival (DSS) of 91% [28]. The 10-year DSS was 65% in SLN-positive patients. GOG 173 was another prospective observational trial where patients with early-stage squamous vulvar cancer with at least 1 mm of invasion and tumors measuring 2–6 cm underwent SLN biopsy followed by inguinofemoral lymphadenectomy [29]. Among 452 patients, at least one sentinel node was identified in 92% of patients. The sensitivity of SLN was 92% and the NPV was 96%. SLN evaluation in patients with prior resection has also been shown to accurately reflect nodal status without impacting oncologic outcome [30].

A systematic review of the various injection techniques suggested peritumoral injections with the use of radiocolloid tracers alone or in combination with blue dye but not blue dye alone because of low detection rates [31]. Complication rates are decreased with SLN biopsy compared with groin LND, with lower rates of wound breakdown (11.7 vs. 34%, respectively) and cellulitis (4.5 vs. 21.3%, respectively) [32]. Long-term morbidity with recurrent erysipelas and lower extremity lymphedema has also been less frequently observed with SLN (0.4 vs. 16.2 and 1.9 vs. 25.2%, respectively).

Ongoing studies are underway to evaluate the role of adjuvant therapy in the setting of positive SLN. The prospective GROINSS-V-II phase 2 study enrolled patients with invasive vulvar cancer less than 4 cm in size with more than 1 mm invasion and no lymphadenopathy on imaging [33▪▪]. Patients with positive lymph nodes received inguinofemoral radiotherapy (IFRT). The trial was amended after 10 patients with positive lymph nodes had groin recurrences – all but one had macrometastatic disease or extracapsular spread. Following the amendment, patients with micrometastases would go on to receive IFRT alone and patients with macrometastases would undergo lymphadenectomy. Among patients with micrometastases treated with IFRT, 1.2% had an isolated groin recurrence at 2 years compared with 12% of patients without IFRT. The 2-year groin recurrence rate was 22% with IFRT vs. 6.9% with LND, with or without radiation therapy ($P = 0.011$). Still, 2-year RFS was similar between the two groups.

OVARIAN CANCER

Sentinel lymph node sampling in ovarian cancer remains investigational. Epithelial ovarian cancer (EOC) predominantly spreads intraperitoneally; however, lymphatic spread has been reported in 14.2% in early-stage disease to approximately 77% in advanced stage disease [34,35]. In the Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) randomized clinical trial, patients undergoing surgical staging were found to have improved outcomes compared with those with incomplete staging (5-year PFS 79 vs. 61% and 5-year OS 89 vs. 71%, respectively), leading to the recommendation of systematic lymphadenectomy in early-stage EOC [36]. Despite this, there has been conflicting evidence regarding the therapeutic value of systematic lymphadenectomy. In the Lymphadenectomy in Ovarian Neoplasms (LION) trial, patients with stage II–IV EOC randomized to systematic lymphadenectomy showed no survival benefit when compared with patients undergoing selective lymph node resection [37].

There is currently no standardized approach to the injection and detection of SLN in ovarian cancer. The most common sites include not only the infundibulopelvic ligament and the utero-ovarian

ligament but also the ovarian cortex and mesovarium [38,39]. The SLN detection rates vary from 40 to 100%, with an overall sensitivity of 66.7% and a 96.6% negative-predictive value [40]. The results of two recent prospective trials to determine the feasibility and accuracy of SLN detection in early-stage ovarian cancer have been presented. The SENTOV study was a single-center trial that included 20 patients with apparent stage I–II ovarian cancer. Oophorectomy was performed, and after frozen pathology confirmed malignancy, technitium-99 and ICG were injected into the infundibulopelvic and utero-ovarian stumps. Pelvic and para-aortic SLN were detected in 93 and 100% of cases, respectively. Contralateral SLN mapping was detected in the para-aortic field in 10% of patients. There were no metastases found in any sentinel or nonsentinel node, limiting the assessment of accuracy in this study [41]. In the Sentinel Lymph Nodes in Early-Stage Ovarian Cancer (SELLY) trial, 31 patients with suspected stage I–II EOC were injected with ICG into the infundibulopelvic and utero-ovarian ligaments [42]. Preliminary results show an overall 67.7% detection rate, with higher rates in women undergoing immediate vs. delayed surgical staging (88.9 vs. 41.7%, respectively). Four patients had positive nodes, and all patients with lymphatic spread had a SLN identified. Sensitivity was 100%, specificity was 100%, false-negative rate was 0%, and the NPV was 100%. The authors concluded that despite the low detection rate, SLN procedure is feasible in early EOC.

CONCLUSION

Sentinel lymph node evaluation is becoming increasingly utilized in gynecologic malignancies. In uterine and vulvar cancer, SLN evaluation is widely accepted as standard of care for select patients. In cervical cancer, it has gained increasing acceptance as a component of surgical management in early-stage disease. In patients with ovarian cancer, SLN evaluation remains investigational. A number of unanswered questions regarding the safety and long-term outcomes of this technique as well as the optimal management of patients with positive SLN particularly those with low-volume disease remain to be addressed and answered.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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