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Review Article

Update on sentinel lymph node biopsy for early-stage vulvar cancer

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HIGHLIGHTS

- SLN is the standard of care for management of early stage vulvar cancer
- preoperative lymphocscintigraphy may be useful
- ultrastaging increases ability to identify nodal metastasis

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ABSTRACT

Two prospective, multicenter clinical trials have demonstrated the feasibility and reproducibility of sentinel lymph node (SLN) biopsy as part of the standard management of early-stage vulvar carcinoma. On the basis of the results of these trials, many gynecologic oncologists have incorporated SLN biopsy for vulvar cancer into their practice. Studies have further shown that SLN biopsy is associated with better quality of life than full lymphadenectomy, is more cost-effective than full lymphadenectomy, and improved pathologic evaluation. A large observational study is currently evaluating the outcomes of patients with early-stage vulvar cancer according to the results of their SLN biopsy and the approach to their care; this study may confirm that full inguinofemoral lymphadenectomy is no longer necessary in most patients with this disease. Here, we review the published data supporting SLN biopsy as part of the standard of care for women with early-stage vulvar cancer and discuss future considerations for the management of this disease.

Contents

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1. Introduction

In 1977, Cabanas pioneered the concept of sentinel lymph node (SLN) biopsy, which was based on his work on penile carcinoma [1]. The rationale for SLN biopsy then was the same as it is today: SLN biopsy provides accurate information about whether cancer has spread to lymph nodes and can spare some patients from undergoing a complete lymphadenectomy. In SLN biopsy, surgeons perform a limited surgery to remove the first lymph nodes that receive drainage from a tumor. Findings on pathologic evaluation of these lymph nodes are then used to determine if an additional, more extensive lymphadenectomy should be performed. While different approaches have been used to identify SLNs, the techniques most commonly used are radioactive tracer injection and "blue dye" injection [2,3]. Since the early work by Cabanas, surgeons who treat breast cancer and melanoma have led the majority of research on SLN biopsy [2,4]. A major driving factor in the development of SLN biopsy has been the desire to spare patients the comorbidities associated with complete lymphadenectomy (e.g., lymphedema).

Squamous cell carcinoma of the vulva (hereafter, "vulvar cancer") is an uncommon gynecologic malignancy; approximately 4850 new cases of vulvar cancer and 1030 deaths from this disease were projected for the United States in 2014 [5]. Surgery remains the primary treatment for early-stage vulvar cancer, but, in the past two decades, the standard of care has shifted from radical to more limited surgery. Previously, treatment of early-stage vulvar cancer involved complete inguinofemoral lymphadenectomy. However, inguinofemoral lymphadenectomy is associated with relatively high rates of postoperative complications: up to two-thirds of patients who undergo dissection of lymph nodes in the groin experience wound breakdown, lymphocyst formation, and/or lymphedema as a result [6–9]. For this reason and because vulvar cancers have a predictable anatomic drainage pattern, lymphatic mapping and SLN biopsy for early-stage vulvar cancer have been studied extensively. SLN biopsy is now the standard of care for selected patients with early-stage vulvar cancer.

2. Why is SLN biopsy the standard of care for early-stage vulvar cancer?

Surgical treatment of vulvar cancer with complete inguinofemoral lymphadenectomy leads to high rates of lymphedema (30%–70%) and wound breakdown (20%–40%). In addition, fewer than one-third of patients have positive nodes, which means that routine inguinofemoral lymphadenectomy exposes a large number of women to potentially avoidable surgical morbidity [10]. The most effective way to minimize morbidity in patients undergoing treatment of vulvar cancer is to minimize disruption of the lymphatic tracts and remove fewer lymph nodes. The benefits of removing fewer nodes, however, need to outweigh the risk of failing to remove metastatic disease in the inguinal region, as nodal recurrence of vulvar cancer is associated with a 75% mortality rate [11].

Several small studies evaluated whether SLN biopsy accurately revealed nodal metastases and was associated with less morbidity than inguinofemoral lymphadenectomy in patients with early-stage vulvar cancer. These small studies culminated in two large trials with very similar results [11,12].

The GROINSS-V study (GROnigen INternational Study on Sentinel nodes in Vulvar cancer) was an observational study of 276 women with early-stage vulvar cancer who had a primary tumor smaller than 4 cm and no metastases detected on SLN biopsy [11]. For patients with unifocal disease, these investigators found a groin recurrence rate of 2.3% over a median follow-up time of 35 months. The false-negative rate was 5.9% (4.6% for patients with unifocal disease), and the false-negative predictive value was 2.9%. This study also demonstrated much lower rates of surgical complications in patients who underwent SLN biopsy alone than in patients who underwent full inguinofemoral lymphadenectomy because of a positive SLN. Rates of complications in patients with SLN biopsy and full lymphadenectomy, respectively, were as follows: wound breakdown, 11.7% versus 34.0%; cellulitis, 4.5% versus 21.3%; recurrent erysipelas, 0.4% versus 16.2%; and lymphedema, 1.9% versus 25.2%. A follow-up survey sent to patients after the GROINSS-V study found that compared to age-matched controls who had undergone complete inguinofemoral lymphadenectomy, women who had undergone SLN biopsy only were more content with their overall status, experienced less edema, and were less likely to need to wear stockings [13].

The Gynecologic Oncology Group (GOG) protocol 173 was a multi-institutional observational study of 452 women with early-stage vulvar cancer [12]. All patients underwent an SLN biopsy followed by a complete inguinofemoral lymphadenectomy. The false-negative predictive value for SLN biopsy was 3.7%. The false-negative rate for SLN biopsy was lower in patients with tumors measuring 2 to 3.9 cm than in patients with tumors measuring 4 to 6 cm (2.0% vs. 7.4%).

On the basis of our experiences (Table 1), we believe that women with vulvar cancer with primary tumors smaller than 4 cm can be counseled preoperatively that if the SLN is negative, the risk of a relapse in the groin due to a false-negative finding on SLN biopsy is less than 3%. Given the results from these two trials, we believe that SLN biopsy should be offered to well-selected patients by well-trained gynecologic oncologists. In clinical settings where vulvar cancer is rare and surgeons' experience is limited, referral to a high-volume center or surgeon is appropriate.

3. Which method of SLN identification provides the best results?

A meta-analysis of studies of SLN biopsy for vulvar cancer demonstrated that the pooled SLN detection rates were 94.0% (95% CI, 90%–96%) for technetium Tc 99 m alone, 68.7% (95% CI, 63%–74%) for blue dye alone, and 97.7% (95% CI, 96%–98%) for 99mTc plus blue dye [14]. In GOG protocol 173, the false-negative rates were 7.8% for radiocolloid alone, 2.0% for dye alone, and 1.6% for radiocolloid plus blue dye [12]. These results provide evidence that a combination of technetium and blue dye is the most accurate technique. Using both technetium and blue dye may also reduce the number of procedures required for a

Table 1
Results summary for GROINSV and GOG 173.

	GROINSS-V	GOG 173
Tumor size	T1 or T2 < 4 cm	T2 (2–6 cm)
Mapping technique	Combined	Initially blue dye, combined
Centers	15	47
Skill verification	10 cases	None
Cases/center (median)	21	6
Primary endpoint	Failure @ 2 yrs. (<8%)	SN: ≥88%, FNPV < 5%
Strategy	IFLN if SLN (+)	IFLN all patients
False negative rate (%)	8/135 patients: 6%	Tumors <4 cm: 6% (8.3% overall)