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Sentinel Lymph Node Evaluation in Vulvar Cancer: The New Standard of Care

Martha Kole and Katina Robison*

Program in Women's Oncology, Department of Obstetrics and Gynecology, Women and Infants Hospital, Alpert Medical School, Brown University, Providence, RI, 02905, USA

***Corresponding author:** Katina Robison, 101 Dudley Street, Program in Women's Oncology, Department of Obstetrics and Gynecology Women and Infants Hospital , Brown University, Providence, RI, USA, Tel: 011-401-274-1100; Fax: 011-401-453-7529; E-mail: krobison@wihri.org

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Abstract

Purpose: The treatment of vulvar cancer remains surgical; however, as surgical treatment has evolved the surgical morbidity has decreased with the use of minimally invasive technology. Sentinel lymph node biopsy, which has been validated in breast cancer and melanoma, has been similarly investigated in vulvar cancer. This review summarizes the current evidence supporting sentinel lymph node biopsy in vulvar cancer.

Findings: Compared to inguinofemoral lymphadenectomy sentinel lymph node biopsy has a sensitivity of 87-92% for the detection of vulvar cancer and a false negative predictive value of 2.0% in tumors ≤ 4 cm. Nodal recurrences following sentinel lymph node biopsies are comparable to recurrence rates following inguinofemoral lymphadenectomy. However complications after sentinel lymph node biopsy, including lymphedema, cellulitis and wound breakdown, are much lower.

Conclusions: Sentinel lymph node dissection is safe and feasible in select patients with vulvar cancers measuring ≤ 4 cm with bilateral SLN dissection for midline lesions. Procedures should be performed at centers with sufficient volume and with radiologists, surgeons and pathologists trained in a sentinel lymph node protocol.

Keywords: Vulvar cancer; Sentinel lymph node; Gynecologic malignancies

Introduction

Sentinel lymph node dissection is a minimally invasive technique that has become the standard of care in numerous cancers and is becoming more heavily utilized in a number of gynecologic malignancies. The use of sentinel lymph node biopsy is based on the sentinel lymph node hypothesis, which assumes that a primary tumor drains to a specific lymph node (or nodes) in the regional lymphatic basin. This validated hypothesis of sequential tumor dissemination has allowed there to be a shift from elective regional lymph node dissections, with its associated morbidity, to less invasive techniques to identify which patients may be candidates for additional surgical or systemic therapy [1,2]. Current research suggests that some women with vulvar cancer should be considered candidates for sentinel lymph node dissection.

Sentinel Lymph Node Dissection

The sentinel lymph node technique was first described in 1977 when it was used in penile cancer to determine the need for deep groin dissection versus no additional surgical therapy [3]. Soon after, this technique was used in the surgical treatment of both breast cancer and melanoma. In 1979 DiSaia et al. described the eight to ten inguinal nodes above the cribiform fascia as "sentinel nodes" and found that when those superficial nodes were free of disease the risk of femoral or pelvic node metastases was remote [4,5].

The concept of sentinel lymph node dissection is based on two basic principles: (1) an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin exists, and (2) the first lymph node functions as an effective filter for tumor cells [1]. Theoretically, if the sentinel lymph node is negative for tumor the remainder of the lymph nodes in the nodal basin should also be negative and may not warrant examination. Allowing for fewer lymph nodes to be removed is one of the greatest benefits of sentinel lymph node dissection.

Sentinel lymph node dissection in vulvar cancer is performed by the injection of a radioactive tracer technetium-99 m sulfur colloid (Tc-99 m) at the tumor edge either the day before surgery or 90-180 minutes prior to surgery [6]. Blue dye is then injected into the tumor edge intraoperatively prior to sentinel lymph node dissection and sentinel nodes are identified intraoperatively as blue or 'hot' nodes using a hand held collimated gamma counter. Sentinel lymph nodes then undergo ultra-staging and are stained with hematoxylin and eosin (H&E).

Vulvar Cancer

Vulvar cancer is the 4th most common gynecologic malignancy accounting for approximately 5% of gynecologic cancers [7]. In 2016 there will be 5,950 new cases and 1,110 deaths attributed to the disease [8]. The mean age at the time of diagnosis is 65 years with over 90% of vulvar cancers being squamous cell subtype [9]. Survival is directly related to groin node involvement, which is the most important prognostic factor, thus making groin node evaluation critical [10,11]. Five year disease specific survival (DSS) decreases with increasing number of positive nodes, with 5-year DSS of 77% in patients with 1 positive node, 62% with 2 to 3 positive nodes and 28% with 4 or more positive nodes [9]. This is in comparison to a 5 year survival rate of 96% in patients with negative inguinal femoral lymph nodes [12,13].

Historically, treatment for vulvar cancer included surgical management with radical vulvectomy and *en bloc* inguinofemoral lymphadenectomy [14]. Unfortunately, these surgeries were associated with high morbidity with approximately 70% of women suffering from chronic lymphedema [13]. Today, although surgery remains the primary treatment for early-stage vulvar cancer the standard of care has shifted to a less invasive triple incision technique with either deep or superficial inguinal femoral node dissection [6,15]. Despite advances in surgical technique to minimize morbidity, complications following treatment for vulvar cancer remain high [11]. The most common complications include lymphedema, lymphocele, wound infection, hematoma, cellulitis or hernia and some studies have indicated that as high as 76% of patients will experience at least one of these complication [11,16]. One review of the literature reported lymphedema in 14-48% of patients, lymphocele formation in 7-40%, wound infection in 21-39%, cellulitis in 21-57%, and wound breakdown in 17-39% of patients following inguinal-femoral lymphadenectomy [11].

While there is a clear need to decrease the morbidity associated with vulvar cancer surgery it is important to identify those women who have positive inguinal femoral lymph nodes and adequately treat them. The current recommendation is that all women with a vulvar cancer with greater than 1mm of invasion should undergo inguinal-femoral lymphadenectomy. However, only 10-15% of early stage vulvar lesions measuring <20 mm will be associated with lymph node metastasis [12,17], and the remaining 85-90% of lesions will have negative lymph nodes. Therefore, by performing sentinel lymph node dissection alone in these women, inguinofemoral lymph node dissection can be saved for those who truly need the procedure.

Sentinel Lymph Node Dissection in Vulvar Cancer

Compared to inguinal-femoral lymphadenectomy sentinel lymph node biopsy has been found to be an accurate method for inguinal node staging in vulvar cancer [18]. A meta-analysis by Hassanzade et al. described sentinel lymph node biopsy to have a sensitivity of 92% compared to inguinal femoral lymphadenectomy and found that the combination of the radio tracer and blue dye led to the highest detection rate of sentinel lymph nodes. A more recent meta-analysis reported a detection rate of 87% for sentinel lymph node biopsy using radio colloid tracer and blue dye [19]. The Gynecologic Oncology Group (GOG 173) performed a prospective multi-institution validation trial for the sentinel lymph node biopsy that concluded sentinel lymph node biopsy is a reasonable alternative to inguinal femoral lymphadenectomy in selected women with squamous cell carcinoma of the vulva [20]. In GOG 173 the sensitivity of sentinel lymph node biopsy was 91.5% and the false negative predictive value was 3.7%.

For patients undergoing sentinel lymph node biopsy for vulvar cancer the most serious safety concern is the risk of groin nodal recurrence as it carries a dire prognosis with five year survival ranging from 0-17% [21,22]. Current literature suggests that groin recurrence is similar in those undergoing sentinel lymph node biopsy compared to inguinofemoral lymphadenectomy [6,23]. A meta-analysis by Covens et al. report recurrence rates for sentinel lymph node biopsy, superficial inguinofemoral lymphadenectomy, and complete inguinal-femoral lymphadenectomy where an attempt was made to remove the deep femoral lymph nodes. Recurrence rates were lowest in the complete inguinal-femoral lymphadenectomy group (1.4%) and highest in the superficial inguinal-femoral lymphadenectomy group (6.6%). Sentinel lymph node biopsy left patients with a recurrence rate of 3.4% [19]. The GROningen International Study on sentinel nodes in Vulvar cancer (GROINSS-V-I) study followed 403 patients with vulvar lesions <4 cm and negative sentinel lymph node biopsy. The actuarial groin recurrence rate after 2 years was 3% (95%CI, 1%-6%) and 2.3% (95%CI 1%-5%) in patients with unifocal disease [23].

Complication rates are dramatically improved following sentinel lymph node biopsy compared to inguinal-femoral lymphadenectomy. The GROINSS-V-I study reported complication rates for patients undergoing sentinel lymph node biopsy only compared those with positive sentinel lymph nodes who underwent inguinofemoral lymphadenectomy. For those who underwent a sentinel lymph node biopsy only the incidence of lymphedema (1.9% *vs* 25.2%), wound breakdown (11.7% vs 34%) and cellulitis were all reduced (4.5% *vs* 21.3%).

In addition to decreased complication rates, sentinel lymph node biopsy provides opportunity for ultrastaging and immunohistochemical staining [19]. With the removal of fewer lymph nodes (1.54 *vs* 9.94) [20] pathologist have more time to focus on ultrastaging, a technique where smaller, serial sections are examined for identification of micro-metastasis measuring less than 2 mm. With fewer lymph nodes additional techniques can also be performed such as immunohistochemical staining. Although these techniques are relatively new and lack uniformity across institutions they certainly add value. Current expert opinion argues that the benefit of increased detection of metastases outweighs potential harms including over-treatment of patients with micro-metastasis, the unclear clinical significance for patients with isolated tumor cells, increased time and financial costs [19].

To identify the appropriate candidates for sentinel lymph node biopsy both lesion size and location should be considered. GOG 173 reported a decreased false negative predictive value (2.0 *vs* 7.4%) as well as a decreased rate of lymph node metastasis (26.4 *vs* 40.9%) in women with primary tumors 2.0 cm to 3.9 cm *vs* 4.0 cm to 6.0 cm. Women with multifocal disease have an increased risk of recurrence and this should be taken into consideration when considering sentinel lymph node biopsy [23]. Lesions within 2 cm of the midline should be treated with caution due to the increased possibility of bilateral lymphatic drainage [24]. In these patients, bilateral sentinel lymph node dissection should be considered as the majority of recurrences seen after sentinel lymph node biopsy are in lesions within 2 cm of the midline [25]. Additional caution should be taken in women who may have altered lymphatic drainage, such as those who have had previous groin surgery [26].

Sentinel lymph node biopsy should be performed at centers with multidisciplinary teams that performs at least 5-10 procedures a year [23]. In the GROINSS-V-I study of the eight patients with false-negative results, four were related to surgeon or procedure-related factors. This highlights the need for strict adherence to a sentinel lymph node protocol including injection of radiotracer, interpretation of lymphoscintigram, involvement of experienced surgeon and pathology department experienced with ultrastaging.

The correct management of patients with positive SLN is currently unknown. The question remains, do all women with positive SLN require a full inguinal femoral lymphadenectomy? GROINSS-V-II/GOG 270 hopes to answer this question by treating women with sentinel nodes metastasis <2 mm with radiation and omitting the inguinal-femoral lymphadenectomy. The addition of chemotherapy is

left to the discretion of the provider. Until that data becomes available, the standard of care remains inguinal femoral lymphadenectomy in women with a sentinel lymph node metastasis of any size.

Conclusion

Utilization of sentinel lymph node technology in vulvar cancer has led to decreased surgical morbidity. Current literature supports the safety and feasibility of sentinel lymph node biopsy when performed at experienced centers in a select group of patients. Patients should be considered for sentinel lymph node biopsy if they have tumors ≤ 4 cm, clinically negative groins, and tumor invasion >1 mm [27]. Multifocal disease should be treated with inguinal femoral lymphadenectomy while patients with midline lesions should undergo bilateral sentinel lymph node biopsy. Currently, if sentinel lymph nodes are positive patients should undergo inguinal femoral lymphadenectomy, though future research may inform this practice.

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