Sentinel Node Mapping in Vulva Cancer

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Abstract

The treatment of early-stage vulvar cancer previously included a complete inguinofemoral lymph node dissection (IFLD). However, IFLD is associated with a substantially high probability of postoperative complications: up to two-thirds of patients who have IFLD performed experience wound infection or breakdown, formation of lymphocytes, or long-term lymphedema. For this reason, lymphatic mapping and sentinel lymph node biopsy (SLNB) for early-stage vulvar cancer have been studied. Compared to IFLD, SLNB has significantly fewer complications and is becoming a more common practice in treatment for selected patients with early-stage vulvar cancer. From our literature review, we discuss SLNB as part of a standard treatment for patients with early-stage vulvar cancer, and we provide future considerations for its use in the management of vulvar cancer.

Keywords

Vulvar cancer • Sentinel nodes • Inguinofemoral lymph node dissection • Early stage • Complication

Contents

1 Introduction

Sentinel lymph node (SLN) identification and lymphatic mapping for vulvar cancer have its origins in cancers of other sites. In 1960, Gould et al. first proposed the concept of a "sentinel node" for head and neck cancer in their description of the key node which was identified at the junction of the anterior and posterior facial vein

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(Gould et al. 1960). In the field of gynecologic cancers, DiSaia et al. first utilized the superficial inguinal lymph nodes as the "sentinel nodes" in the treatment of vulvar cancer to help them identify patients who would not benefit from a more morbidity-causing complete IFLD (DiSaia et al. 1979). In the 1990s, Morton et al. described what is now the new procedure lymphatic mapping in the treatment of melanoma, in which blue dye was used to identify the primary lymphatic drainage basin (Morton et al. 1992).

The premise of SLN biopsy (SNLB) is that tumor cells from the primary lesion will first migrate "downstream" in the lymphatic flow to one or a few key lymph nodes, prior to disseminating to other regional lymph nodes. These key lymph nodes can be identified by using either a vital blue dye (isosulfan blue/methylene blue), a radiocolloid, or indocyanine green (ICG). Key to the utilization of this technique is confidence that identification of the SLN accurately predicts the status of the remaining lymph nodes.

Surgery still remains the primary care for early-stage vulvar cancer, but in the past two decades, the standard treatment has made a transition from radical dissection to minimally invasive surgery. Primarily, the surgical treatment of early-stage vulvar cancer includes a complete inguinofemoral lymph node dissection (IFLD). However, IFLD is associated with a significantly high probability of postoperative complications; up to two-thirds of patients who have had extensive dissection of inguinal lymph node performed experienced wound infection or breakdown and lymphocyst formation or long-term lymphedema after surgery (Stehman et al. 1992; Gaarenstroom et al. 2003; Rouzier et al. 2003; Kirby et al. 2005). Because of this high morbidity, and since vulvar cancer is an excellent target for the SLN concept, the tumor is easy to inject with blue dye or radiocolloid. Because the lymph drainage is predictably to one or both of the groins, lymphatic mapping and SLNB for early-stage vulvar cancer have been widely studied as a possible alternative procedure to current IFLD procedures. As a result of those studies, SLNB has now become more common in the treatment for selected patients with early-stage vulvar cancer.

2 Patient Selection for SLNB Versus IFLD

As mentioned above, IFLD is associated with a high morbidity rate, including a 20–40% risk of wound complications and a 30–70% risk of lower extremity lymphedema. In addition, fewer than one-third of early-stage vulvar cancer patients have lymph node metastasis, which means that the routine application of IFLD exposes a large number of patients to potentially preventable surgical complications (Sedlis et al. 1987).

The most effective way to minimize morbidity in patients where surgical treatment of vulvar cancer is performed is to minimize damage of the lymphatic tracts by removing fewer lymph nodes. The benefits of dissecting fewer nodes, however, must outweigh the risk of failing to remove actual metastatic lymph nodes in the inguinofemoral region, as inguinal and pelvic recurrence of vulvar cancer is associated with a 27% 5-year survival rate (Maggino et al. 2000).

Two large trials have evaluated whether SLNB accurately detected positive lymph node and whether SLNB reduced morbidity as compared with IFLD in patients with early-stage vulvar cancer (Van der Zee et al. 2008; Levenback et al. 2012). The GROINSS-V study was an observational study of 276 patients with squamous cell cancer of the vulva, with T1/T2 (<4 cm) and no lymph node metastases detected on SLNB (Van der Zee et al. 2008). Study investigators found that patients with multifocal disease had a higher recurrence rate after SLNB (11.8%) compared with patients with unifocal disease (2.3%). The false-negative rate for SLNB of multifocal disease was 5.9% (4.6% for patients with unifocal disease), and the false-negative predictive value was 2.9%. This study suggested it was less common for surgical morbidity in patients who underwent only removal of SLN, compared with patients with a metastatic sentinel node who subsequently underwent IFLD. Wound breakdown, cellulitis, lymphedema, and recurrent erysipelas are also significantly less after SLNB compared to IFLD. A follow-up survey sent to patients after the GROINSS-V study found that no difference in overall quality of life was observed between the

two procedure groups and that the major difference found was the increase in complaints of lower extremity lymphedema after IFLD (Oonk et al. 2009).

The Gynecologic Oncology Group (GOG) Protocol 173 was a multi-institutional observational study of 452 patients with early-stage vulvar cancer (Levenback et al. 2012). All patients underwent intraoperative lymphatic mapping and SLNB, followed by IFLD. The overall false-negative rate for SLNB was 3.7%. However, the false-negative rate for SLNB was much lower in women with tumors smaller than 4 cm than in women with tumors 4–6 cm (2.0% vs. 7.4%). In addition, the location of the tumor was another important factor found in a systematic review (Hassanzade et al. 2013). For lesions which were within 2 cm of the midline, the detection rate was considerably lower compared with more lateral lesions greater than 2 cm from the midline plane (73% vs. 95%).

From this evidence, we suggest that patients with early-stage vulvar cancer, with primary tumors that are unifocal and smaller than 4 cm and where the lesion(s) are located more than 2 cm from the midline, can be assured preoperatively that, if the SLNB is negative, the risk of a recurrence of the inguinal lesion is less than 3%. Given the cumulative results from these studies, we feel confident that the SLNB can be offered to patients carefully selected by skilled gynecologic oncologists. In clinical practices where vulvar cancer is rarely encountered and experience of the surgeon with the disease is negligible, referral to a high-volume center and a more experienced surgeon is recommended.

3 Drainage Tracer

In the GOG Protocol 173, the false-negative rates for SLNs identified by dye and radiocolloid, dye alone, and radiocolloid alone were 1.6%, 2.0%, and 7.8%, respectively (Levenback et al. 2012). A meta-analysis of 29 studies of SLNB for vulvar cancer found that the pooled SLN detection rates were 94.0% for 99mTc, 68.7% for blue dye alone, and 97.7% for combined 99mTc and blue dye (Meads et al. 2014). These results demonstrate evidence that a combination of radiocolloid and blue dye is the most sensitive for detecting SLN. Because of the direct visualization of the lymphatic mapping for vulvar cancer provided by using blue dye, using the combination of radiocolloid and blue dye may also improve the learning curve for the SLNB procedure.

In recent years, near-infrared (NIR) fluorescence imaging has been introduced in lymphatic mapping and SLNB for vulvar cancer. The NIR technique has the potential for far more accurate and real-time intraoperative SLN mapping. A meta-analysis of SLNB with NIR fluorescence imaging in vulvar cancer has reported a good outcome, with a high detection rate of inguinal lymph node metastasis (91.4%) and a considerably higher negative predictive value (100%) (Handgraaf et al. 2014). However, the penetration capacity of NIR fluorescence is limited to approximately 8 mm. The use of radiotracers therefore remains indispensable, since it allows preoperative scintigraphy and intraoperative identification of deep SLN in the groin. Further studies will therefore be needed to compare the effectiveness of ICG with radiocolloid injection versus the traditional combination approach of blue dye and radiotracer.

4 Ultrastaging

Ultrastaging is the term used to describe intense histologic examination of the SLN samples. Ultrastaging is unrealistic in the daily practice setting and is thus rarely performed because it is an onerous task to examine the, on average, ten lymph nodes per groin removed by conventional IFLD. In contrast, ultrastaging is amenably performed on the 1–2 lymph nodes per groin obtained by SLNB. The combination of hematoxylin-eosin (H&E) and cytokeratin immunohistochemical (IHC) staining of paraffin-embedded SLN tissue that is sectioned every 0.4 to 0.5 mm intervals (as contrasted with the 2 to 3 mm section intervals used for traditional lymph node evaluations) has led to the identification of micrometastases in SLN otherwise

thought to be void of lymph node metastasis by conventional pathologic examination. IHC staining should thus be added to H&E staining for more accurate identification of micrometastases.

In GOG Protocol 173, 23% of all SLN were detected to be positive by immunohistochemistry when the routine H&E staining did not reveal metastatic disease (Levenback et al. 2012). In the GROINSS-V study, the authors reported that, of 135 positive SLN in 403 patients, 80 (59%) were detected with routine sectioning and H&E staining, 19 (14%) were detected by ultrastage sectioning using H&E staining, and a further 36 (27%) positive SLN were detected by ultrastaging with immunohistochemical staining. The risk of a non-SLN metastases was higher when the SLN was found positive by routine histological assessment than by ultrastaging (27.1% vs. 5.4%) (Oonk et al. 2010). In patients with SLN metastasis identified by ultrastaging, the 5-year overall survival rate was higher than in patients with SLN metastasis identified by routine pathological examination (89% vs. 65%).

Without examination of the lymph nodes removed by SLNB or full IFLD by the same pathological evaluations, it will be difficult to confirm the true value of the detection of micrometastases by ultrastaging of SLN. A better consensus on the standards for pathological evaluations and the need for ultrastaging is required.

5 Recurrence Rate

Recurrence of vulvar cancer in the groin is usually a fatal event, making it an important outcome measurement for this patient population. IFLD patients were historically divided into two groups: superficial and complete resection. Complete resection was used to describe an inguinofemoral lymphadenectomy combined with removal of the deep femoral lymph nodes, while superficial resection was used to describe procedures without an attempt to remove the deep femoral lymph nodes. Using complete resection, the lowest reported rate of groin recurrence following IFLD was about 1%. However, rates of surgical morbidity, especially wound breakdown and lymphedema, were excessively high (Stehman et al. 1992).

In the case of superficial resection, inguinal recurrence rates of 5–7% were seen and were considered less acceptable compared with historical controls (Robison et al. 2014). For SLNB, the groin recurrence rate was expected to be less than 3%. For well-selected patients with vulvar cancer, this result seems to be an acceptable compromise that minimizes surgical morbidity. Of course, for a tailored treatment in a clinical situation, the informed consent procedure for SLNB for vulvar cancer needs to include as a possible option a full IFLD. For patients with a 1 cm squamous cell carcinoma with less than 2 mm of stromal invasion, the risk of recurrence is approximately 1%, if the SLN is negative for metastasis. In contrast, for patients with a 4 cm or larger vulvar cancer, accompanied deep stromal invasion, the risk of recurrence is significantly higher, even if the SLN is negative for metastasis.

6 Survival Rate

Regardless of the type of lymphadenectomy, an inguinal recurrence of vulvar cancer worsens the survival rate (Martinez-Palones et al. 2006; Terada et al. 2006; Moore et al. 2008; Van der Zee et al. 2008; Oonk et al. 2010). Achimas-Cadariu et al. reported that the median overall survival period was 61.2 months but was only 16.2 months for patients who experienced a relapse (Achimas-Cadariu et al. 2009).

The GROINSS-V study is the largest investigation to date into the disease-specific survival rate among patients with no detected metastases by SLN (Van der Zee et al. 2008). At a median follow-up time of 35 months, the 3-year disease-specific survival rate among patients with unifocal vulvar disease and a negative SLN was 97.0%. The 3-year disease-specific survival for patients

with sentinel node metastases larger than 2 mm was lower than for those with metastases 2 mm or smaller tumors (69.5% vs. 94.4%) (Oonk et al. 2010).

7 Complications

Surgical complications for vulvar cancer include wound infection, wound breakdown, lymphocele, and long-term lymphedema. However, wound complications have decreased dramatically since the implementation of the "separate groin incision" technique (Wills and Obermair 2013). A recent systematic review regarding complication rates of IFLD reported that lymphedema occurs in 14–48% of patients after groin dissection, lymphocele formation in 7–40%, wound infection in 21–39%, and wound breakdown in 17–39% (Wills and Obermair 2013). Estimates for complications following an SLNB and IFLD were reported in the GROINSS-V study. For SLNB and IFLD, the wound breakdown rate was 11.7% vs. 34%, cellulitis was 4.5% vs. 21.3%, and lymphedema was 1.9% vs. 25.2%, respectively (Van der Zee et al. 2008). The results of the Levenback et al. (2012) validation study (GOG Protocol 173) demonstrated similar results to the GROINSS-V study (Van der Zee et al. 2008).

8 Quality of Life

IFLD, particularly when it is followed by radiation or chemoradiation, can aggravate the patient's quality of life (QOL). One study (62 patients) investigating QOL with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) found few differences between SLNB and IFLD; only the score regarding financial difficulties was significantly worse in the IFLD group. For the FACT-V questionnaire, there were significantly worse results for the scales concerning contentment functional, lymphedema, and complaints and stockings symptoms (Oonk et al. 2009).

Novackova et al. observed increased fatigue and more impaired lymphedema in patients with vulvar cancer after IFLD, compared with those after SLNB (Novackova et al. 2015). Forner et al. found that IFLD had a negative influence on the patients' sexual function (Forner et al. 2015). Additional studies are required to see how SLNB versus IFLD impact QOL in patients with vulvar cancer.

9 Cost-Effectiveness of SLNB

Erickson et al. compared the costs of SLNB with IFLD (Erickson et al. 2014). Their analysis concluded that SLNB is the most cost-effective strategy for the management of patients with early-stage vulvar cancer due to lower treatment costs and lower costs due to complications. Although there are additional costs associated with SLNB, including tracer injections, intraoperative mapping, imaging, and ultrastaging, these costs are offset by a shorter hospitalization. While both management strategies have similar disease-free survival estimates, the difference in treatment costs is approximately $4000 more for the IFLD per patient than for SLNB.

McCann et al. also reported a similar cost-effective analysis of SLNB and IFLD (McCann et al. 2015). Their analysis discovered that SLNB was less costly than IFLD ($13,449 vs. $14,261) and more effective for quality of life (4.16 quality-adjusted life years (QALYs) versus 4.00 QALYs). In this study, variations in the rate of positive SLNB and probability of lymphedema over clinically reasonable ranges did not alter the results. In their study, the increase in lymphedema associated with IFLD played a major role in the differences the costs between SLNB and IFLD.

SLNB is associated with shorter surgical time, fewer postoperative complications, and lower costs associated with postoperative complications. The incidence of lymphedema following IFLD are reported to be much higher, as high as

67% in one prospective study (Carlson et al. 2008). Among patients where only SLNB was performed, the morbidity rate was 1.9% (Van der Zee et al. 2008).

10 Learning Curve for Conducting SLNB

Vulvar cancer is a rare condition and the SLNB for it is a technically challenging procedure for surgeons. Acquiring experience in identifying the SLN accurately in patients with vulvar cancer is a very significant challenge. Schutter et al. describe the SLNB procedure as a complex interaction process between clinicians, specialists in nuclear medicine, and pathologists. So, if this interaction is ever inadequate, SLNB of vulvar cancer could have lethal consequences (Schutter and van der Sijde 2014). Given the strong potential for variations in operator skill in identifying SLN, an expert panel convened in 2008 recommended that a gynecologic oncologist performed at least ten consecutive cases with successful SLN identifications and no false-negative results before performing stand-alone SLNB without lymphadenectomy (Levenback et al. 2009).

While surgeons participating in the GOG Protocol 173 were not required to have a specific level of experience in conducting SLNB, surgeons participating in the GOG Protocol 270 were (GROINSS-V II study). Studies often define the first ten cases as part of the learning curve, after which SLNB without IFLD could be performed (Hampl et al. 2008; Van der Zee et al. 2008). Levenback et al. calculated that the rate of failure to identify an SLN was worse during the first 2 years of the study (16% in the first 2 years and then 7% for subsequent years) (Levenback et al. 2012).

Klapdor et al. reported that single-photon emission computed tomography (SPECT/CT) leads to higher SLN identification compared to lymphoscintigraphy in vulvar cancer (Klapdor et al. 2015). Due to its higher spatial resolution and three-dimensional anatomical localization of SLN, the number of cases required to become a skilled surgeon in SLNB for vulvar cancer may be reduced by the use of preoperative SPECT/CT and by observing other surgical oncologists as they perform SLNB for breast cancer or melanoma (Chapman et al. 2016).

11 Conclusion

The development of SLNB in treatment for vulvar cancer has involved an unprecedented level of cooperation among investigators in Europe and the United States. SLNB is recommended for patients with early-stage vulvar cancer with primary tumors that are unifocal and smaller than 4 cm with clinically non-suspicious lymph nodes of metastasis in the groin, provided there is specific infrastructure with well-skilled surgeons. Some recommendations for appropriate techniques and procedures are also provided. Further recommendations on the management of patients with SLN metastasis are currently pending until the results are available from the GOG Protocol 270, which will incorporate the next phase of the GROINSS-V study (GROINSS-V II study). The purpose of this latter study is to investigate whether the dissection of SLN followed by chemotherapy and/or radiation is effective in managing early-stage vulvar cancer.

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