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MINIREVIEWS

Evaluation of sentinel lymph nodes in vulvar, endometrial and cervical cancers

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Abstract

Sentinel lymph node (SLN) biopsies are a sensitive tool in evaluating lymph nodes for multiple cancers, and in some diseases they decrease morbidity in both the short- and long-term. SLN detection in gynecologic malignancies has been studied extensively over the past decade. We review the current literature on SLN dissection in vulvar, endometrial and cervical cancers. Large, well-designed trials in each of the three types of cancer have demonstrated high sensitivity and low false-negative rates when SLN biopsy is performed in the correct patients and with an appropriate technical approach. In all of these cases the addition of ultra-staging to conventional pathology yields increased detection of micrometastatic disease. Biopsy of the sentinel nodes is feasible and safe in early vulvar malignancies, with multiple studies describing low recurrence rates in those women who have with negative SLNs. There does not appear to be a survival benefit to lymphadenectomy over SLN biopsy and quality of life is improved in women undergoing SLN biopsy. Optimal treatment strategies for women with positive nodal biopsies, particularly in cases with micrometastatic disease, remain unclear. Multiple large studies investigating the utility of SLN biopsy in endometrial malignancy have found that sentinel nodal status is a reliable predictor of metastases in women with low-risk disease. Prospective studies are ongoing and suggest sentinel nodal detection may soon become widely accepted as an alternative standard of care for select cases of endometrial cancer. In cervical cancer, SLN biopsy is accurate for diagnosing metastatic disease in early stage tumors ($\leqslant$ 2 cm diameter or stage $\leqslant$ IB2) where the risk of metastasis is low. It is unknown if women who undergo SLN biopsy alone will have different survival outcomes than women who undergo complete lymphadenectomy in these cases. In a specific population of women with vulvar cancer, SLN dissection is an effective and safe alternative to complete dissection. It can be offered as an alternative management strategy in these women. In women who do undergo SLN biopsy, it is associated with improved quality of life. Promising evidence supporting the utility of SLN dissection in endometrial and cervical cancer continues to emerge, and it may soon become a reasonable option for select patients. However, continued research and refinement of appropriate patient selection and long-term follow-up are necessary.

Key words: Gynecologic malignancies; Sentinel lymph node; Endometrial cancer; Cervical cancer; Vulvar cancer

Core tip: In a specific population of women with vulvar cancer, sentinel lymph node (SLN) dissection is an effective and safe alternative to complete dissection. It can be offered as an alternative management strategy in these women. Sentinel node biopsy is also associated with an improved quality of life. Promising evidence supporting the utility of SLN dissection in endometrial and cervical cancer continues to emerge, and it may soon become a reasonable option for select patients. However, continued research and refinement of appropriate patient selection and long-term follow-up are necessary.

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INTRODUCTION

Sentinel lymph node (SLN) biopsy has become the standard of care in multiple non-gynecologic malignancies. As a surgical technique, SLN biopsy was initial developed for the treatment of penile cancer in 1977, and was adopted into treatment strategies for breast cancer and melanoma shortly thereafter[1]. The SLN is the first node within a lymphatic chain which drains the primary tumor. As the first in a chain of lymph nodes, theoretically the sentinel node will be the first to receive metastatic disease. If the sentinel node is negative then, it is assumed that the remainder of the lymphatic basin is also without metastatic disease. One of the distinctive benefits of SLN biopsies is the opportunity to avoid "over-staging", the removal and dissection of non-diseased tissues in an effort to identify the extent of a patient's cancer. Furthermore, with fewer lymph nodes to examine, pathologists can performed more in-depth analysis on the relatively smaller volume of available tissues.

Application of SLN biopsy techniques in gynecologic malignancies has been studied extensively over the past decade as nodal dissections in these cancers can lead to long-term morbidities. In breast and vulvar cancers SLN biopsy is predictive of the disease status of the lymphatics and has demonstrated decreases in the significant short and long-term morbidities which are seen in complete lymphadenectomy. However, sampling of the SLN in other gynecologic malignancies is still investigational. We will review the continually growing body of literature supporting SLN biopsy in the treatment of vulvar cancer, as well as reviewing the current evidence behind the use of SLN biopsy in endometrial and cervical cancers.

VULVAR CANCER

Vulvar cancer is relatively uncommon, accounting for 5% of gynecologic malignancies[2]. Five thousand one hundred and fifty new cases of vulvar cancer and 1080 deaths attributable to the same are anticipated in the United States in 2015[2]. Traditional radical vulvectomy with en bloc inguinofemoral lymphadenectomy was associated with high morbidities including 70% of women suffering from chronic lymphedema[3]. Over time, in order to minimize surgical morbidity, the standard of care has shifted. It is now standard practice to perform vulvectomy or radical wide local excision, with deep or superficial inguinal femoral node dissection, instead of radical vulvectomy. Unfortunately, even with this less radical surgery complication rates remain significant. A 2013 review of complications in inguinal femoral nodal dissection reported lymphedema in 14%-48% of patients and formation of lymphocele in 7%-40% of patients. Furthermore they report wound infections in 21%-39% of patients, cellulitis in 21%-57% and wound breakdown in 17%-39% of cases[4]. This significant morbidity has lead to the development of less invasive and less morbid methodologies, particularly the use of SLN biopsy. Indeed, at experienced centers and with select patients SLN sampling is the new standard of care[5].

Survival rates in vulvar cancer are highly dependent upon inguinal femoral lymph node status; thus their evaluation is critical[6]. Five-year survival rates are 96%, 80% and 12% in women with negative inguinal femoral lymph nodes, two or less positive lymph nodes and more than two positive lymph nodes, respectively. Survival continues to falls significantly with increasing numbers of positive nodes beyond 2[7]. However, the majority of women that undergo lymphadenectomy will not have nodal disease. It has been shown that tumor size is prognostic of the risk of lymph node metastases with only 10%-15% of patients with vulvar tumors less than 20 mm having inguinal femoral metastases[6,8]. This suggests that up to 90% of patients could be spared the morbidity of complete lymphadenectomy if appropriately identified.

Levenback *et al*[9] first described the application of SLN biopsy in vulvar malignancy, adopting technical features from the melanoma literature[9,10]. Multiple subsequent studies have demonstrated the safety, feasibility and low false negative rates of SLN biopsy in these patients[10-15]. The majority of studies use a dual-injection approach with pre-operative radioactive tracer injection of technetium-99 sulfur colloid (^{99m}Tc) and isosulfan or methylene blue injection in the operating room[16].

A systematic review published in 2015 by Covens *et al*[17] reported high rates of sentinel node detection and low false-negative rates. Although they report significant variability among studies, the overall detection rate was 86.9%. Twenty five studies analyzed in this review reported SLN biopsy followed by inguinal femoral nodal dissection; the false negative rate for sentinel node biopsy among these studies was 6.6%[17].

GOG 173 was a large prospective multicenter trial comparing SLN biopsy to inguinal femoral lymphadenectomy. Four hundred and fifty-nine patients with tumors between 2 and 6 cm and without signs of affected lymph nodes on clinical exam were included in the trial. All women underwent lymphatic mapping using radioactive tracer and blue dye. SLN biopsy was performed when possible, followed by complete lymphadenectomy. One or more SLN was found in 412 women, and 132 (31.6%) had lymph node metastases. Sensitivity and false-negative predictive value (FNPV) were 91.7% and 3.7%, respectively. Both were impacted by the size of the tumor; in those lesions less than 4 cm in diameter the FNPV was 2%, while it rose to 7.4% when size ranged from 4-6 cm[18]. Another large multicenter study, conducted by Hampl *et al*[19], evaluated accuracy and feasibility of SLN biopsy in women with T1-T3 vulvar cancer. They reported a 98% detection rate, 92.3% sensitivity and 7.7% false negative rate[19].

This study included patients with large lesions (> 4 cm), and a wide range of experience in SLN biopsy among participating surgeons, likely contribute to the higher false negative rate.

One of the distinct advantages of SLN biopsies is the opportunity for ultra-staging. Levenback *et al*[18] found that the mean total of lymph nodes resected with complete inguinal femoral dissection was 8.94, as compared to a mean of 1.54 lymph nodes with sentinel biopsy. With fewer nodes, the pathologist can focus efforts on examining smaller, serial sections, a technique known as ultra-staging. Pathologic examination of a SLN is likely to identify smaller metastases to these nodes. Those metastases measuring 0.2-2 mm in size are referred to as micrometastases, and while their clinical significance is not entirely understood in all gynecologic cancers they have been identified as predictors of relapse in melanoma and breast cancer. In addition, techniques such as immunohistochemical staining and reverse-transcriptase polymerase chain reaction analysis for cytokeratin expression can be added to hematoxylin and eosin staining to potential increase tumor cell detection rates[20]. Studies evaluating the impact of these methods on detection of metastatic tumor cells are varied and report a range of results. However, this is at least partially due to a lack of uniform techniques used across institutions[21]. Current expert opinion argues that the potential benefit provided by ultra-staging and immunohistochemical staining of sentinel nodes outweighs the risks of increased time, cost, and identification and treatment of metastases of uncertain clinical significance[17].

Initial studies evaluated SLN biopsy followed by complete nodal dissection. However, the large multicenter GROningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V-I) was the first to evaluate the safety of SLN biopsy alone.

Inclusion in this multicenter observational study required that patients have unilateral and unifocal tumors of the vulva smaller than 4 cm in diameter; only squamous cell cancers were included. Women with negative SLN evaluation following completion of ultra-staging underwent serial surveillance, while those with positive SLN underwent inguinal femoral lymphadenectomy. Of the 403 patients enrolled, 276 had negative SLNs. During a median follow-up period of 35 mo there were 8 episodes (2.9%) of groin recurrence. Furthermore, the investigators found a decrease in morbidity for patients who had only SLN biopsy when compared to women who underwent complete nodal dissection. Perhaps the best illustration of this is in the incidence of postoperative lymphedema. Less than 2% of women who had only SLN biopsy experienced lymphedema, compared to 25.2% of women who underwent complete lymphadenectomy[22].

Unfortunately, groin nodal recurrence of vulvar cancer carries a dire prognosis, with 5 year survival rates ranging from 0%-17%[23,24]. In their meta-analysis, Covens *et al*[17] included an analysis of recurrence rates when women were followed after SLN biopsy, superficial inguinal nodal dissection, or complete nodal dissection (involving dissection of the deep femoral lymph nodes). Twenty-three studies were included, with a broad range of follow-up durations. They reported a 6.6% (4.4-9.0) recurrence rate in women undergoing superficial nodal dissection and a 1.4% (0.4-2.9) recurrence rate with complete inguinal femoral dissection. Comparatively, the recurrence rate with sentinel node biopsy was between these two values, at 3.4% (1.8-5.4)[17].

Identification of appropriate patients for sentinel node biopsy instead of complete inguinal femoral lymphadenectomy is another important factor. GROINSS-V-I reported an increased risk of recurrence in women with multifocal disease (11.8% *vs* 2.3%), suggesting that sentinel nodal biopsy is likely inadequate in this subset of patients[22]. Tumor size is another important predictor of nodal metastases. The largest studies evaluating SLN biopsy excluded patients with clinically suspicious nodes, and most would recommend complete groin lymphadenectomy in this group of patients[22]. GOG 173 demonstrated differences in both the rate of nodal metastasis and the false-negative SLN biopsy rate when comparing tumors of different sizes. In women with tumors measuring 2.0-3.9 cm the rates of nodal metastasis and false-negative SLN biopsy were 26.4% and 2%, respectively. Comparatively, women with tumors measuring 4-6 cm had nodal metastasis in 40.9% of cases and the false-negative rate was 7.4%[25]. Furthermore, tumors near the midline have increasing odds of bilateral lymphatic drainage, with

tumors located < 2 cm from the midline accounting for the majority of recurrences after SLN biopsy[26].

Much of the research on SLN biopsy began as an effort to decrease morbidity from the surgical management of vulvar malignancy, which raises the question "Is quality of life (QoL) better for women that undergo SLN biopsy alone?". While all studies have shown decreased treatment related morbidity with SLN biopsy, a few studies have also shown that SLN biopsy improves overall QoL for women who undergo SLN biopsy compared to women who undergo complete groin lymphadenectomy[27-29].

Questions of the cost-effectiveness of SLN biopsy have also been raised; the short-term increased costs associated with an additional surgical technique and possible increased risk of recurrence must be weighed against the longer term impacts that complete inguinal femoral lymphadenectomy have on both healthcare expenditures and quality of life. A cost-effectiveness model evaluating SLN biopsy in vulvar cancer found that SLN biopsy was both less costly and more effective than complete lymph node dissection. Only when the model was altered in such a way that lymphedema did not negatively impact quality of life, did complete inguinal lymphadenectomy become a cost effective option[30].

Although there is a significant body of literature to verify the safety and feasibility of SLN biopsy in vulvar squamous cell cancer, the appropriate treatment in women with a positive sentinel node remains uncertain. The currently recruiting GROINSS-V-Ⅱ/GOG 270 study aims to answer this question, treating women with positive sentinel nodes with radiation plus or minus chemotherapy, eliminating the complete inguinal femoral dissection. However, until those results become available, the standard of care remains complete dissection in the setting of nodal metastases. This is based upon GROINSS-V-Ⅰ data demonstrating that when there is sentinel node metastasis present there is an unacceptably high risk of additional metastasis beyond that node, regardless of metastasis size[31].

A 2008 statement issued by the International Sentinel Node Society states that SLN biopsy should be offered to patients with clinical stage Ⅰ-Ⅱ vulvar cancer when "the SLN biopsy is performed by a skilled multidisciplinary team in well-selected patients." We feel that SLN biopsy is appropriate when the tumor is ⩽ 4 cm in diameter**,** there is no clinical evidence of groin involvement, and invasion is > 1 mm[16,32]. Additionally, midline lesions necessitate bilateral SLN biopsy, and patients with multifocal tumors should undergo complete inguinal femoral dissection[22]. Furthermore, surgeons should demonstrate their ability to identify sentinel nodes before offering this technique to patients. This can best be accomplished by performing SLN biopsy with a standard technique followed by concurrent total lymphadenectomy[22,32]. The panel recommended that before utilizing SLN biopsy alone surgeons should successfully identify a SLN in ten successive cases, without any false-negatives[32]. Unfortunately, the infrequent occurrence of vulvar cancer may make the necessary volume difficult to achieve for many gynecologic oncologists. Due to this low volume, some suggest that vulvar cancer is best treated in a limited number of specialized referral centers where patients can best benefit from maximally trained and experienced surgeons[17].

ENDOMETRIAL CANCER

An estimated 54870 new cases of endometrial cancer will be diagnosed in the United States in 2015, making it the most common of the gynecologic malignancies[2]. For the majority of newly diagnosed patients management includes complete surgical staging, which includes pelvic and para-aortic lymphadenectomy. Lymph node status is an important prognostic element in endometrial cancer, making lymphadenectomy a central factor in the initial treatment[33]. However, lymphadenectomy is not without risk. Low-risk patients undergoing lymphadenectomy experience increased morbidity, cost and operating room time without associated survival benefit[34]. Only about 10% of women with clinical stage Ⅰ cancer will have disease-positive lymph nodes, and in women with superficial invasion and well differentiated tumors the rate of lymph node involvement falls to 3%-5%[35,36]. This indicates that 95%-97% of women with early stage cancer will have negative lymph nodes. However, inadequate staging often leads to increased postoperative therapy, particularly external beam radiation in "under-staged" individuals[37]. Given this clinical conundrum a less invasive approach for the evaluation of nodal basins may offer significant benefit.

A number of contemporary studies have now outlined the validity of lymphatic mapping in endometrial cancer. The SENTI-ENDO trial published in 2011 was a prospective multicenter cohort study assessing detection and accuracy of sentinel node biopsy in early endometrial malignancy. One hundred and thirty-three women underwent lymphatic mapping *via* intracervical injection of both ^{99m}Tc and blue dye, followed by complete pelvic nodal dissection. Sentinel nodes underwent more rigorous pathologic evaluation than non-sentinel nodes, with immunohistochemistry and ultra-staging. The negative predictive value and sensitivity for detection of metastatic disease in the lymph nodes were 97% and 84%, respectively. Of the three false-negative results, two were located in the contralateral pelvis and one was in the para-aortic nodes. There were no major adverse outcomes associated with the SLN biopsy approach[35]. This study successfully demonstrated that sentinel nodal status in endometrial cancer accurately predicts nodal metastatic disease.

More recently, Barlin *et al*[38] published the outcomes of their systematic and stepwise approach to lymphatic mapping and SLN biopsy. The algorithm involves universal evaluation of the serosa and peritoneum, excision of mapped SLNs, excision of any non-sentinel clinically suspicious nodes, and a hemi-pelvic complete

node dissection on each side where no SLN is identified. In their study of 498 patients, 81% had at least one sentinel node. Thus, 19% required bilateral pelvic nodal dissection and 30% required unilateral nodal dissection. Using this approach they reported a false-negative rate of 2%, sensitivity of 98.1% and negative predictive value of 99.8%[38]. This process for evaluating pelvic nodes provides a notable improvement in the yield of SLN biopsy while still leading to adequate lymph node evaluation in patients without successful bilateral lymphatic mapping.

In endometrial cancer, the SLN technique varies between institutions. There are three primary SLN injection protocols used. It is important to note that the lymphatic drainage of the uterus is bilateral, and as such identification of lymph nodes on both sides of the pelvis is a key factor in the potential success or failure of any SLN detection approach. Injection modalities include intracervical injection, injection into the uterine serosa, and injection into the endometrium *via* hysteroscopy. A 2011 meta-analysis found the greatest detection rates with intracervical injection, although this result was not statistically significant[39]. The majority of large studies published since employed intracervical injection. Ease of access, ease of injection, anatomic plausibility for accurate mapping, and low frequency of distorting factors such as myomas or scar tissue from cervical procedures in patients with endometrial cancer have all been cited as reasons to favor cervical injection[40].

Furthermore, three types of injected tracers, used alone of in combination with one another, provide variation between the published protocols and their results. Blue dye, ^{99m}Tc and indocyanine green (ICG) have all been shown to be efficacious in lymphatic mapping. The most prevalent strategies currently appear to be blue dye in combination with ^{99m}Tc, or ICG alone. Bilateral detection rates with the dye and ^{99m}Tc combination have ranged from 66%-69%[41-43], while ICG ranges from 60%-79%[44-46]. A recent cohort study comparing successful mapping with either blue dye or ICG found a significant improvement in bilateral SLN detection with ICG. Additionally, patient BMI was a predictor of failed mapping with blue dye, while BMI did not impact mapping with ICG[45]. This is an important difference given the prevalence of obesity in women with endometrial cancer. How *et al*[43] published on the approach of combining all three agents into one injection, and in a cohort of 100 patients reported a bilateral detection rate of 76%.

Importantly, lymphatic mapping can identify sentinel nodes in areas which would not have been sampled with conventional lymphadenectomy and are three times more likely to contain metastases than non-sentinel nodes[40]. Jewell *et al*[46] reported reported slightly more than 10% of patients in their study had sentinel nodes located outside of the pelvic basin, primarily in the para-aortic region. Others report identifying significant numbers of nodes in the pre-sacral region, parametria and the hypogastric vein with lymphatic mapping[43]. Expanding the field of dissection in the presence of variant drainage channels is generally done only when variance is identified, as is the case with lymphatic mapping.

The previously described studies pertain to patients with early stage disease. The Survival Effect of Para-aortic Lymphadenectomy in Endometrial Cancer study retrospectively evaluated overall survival in patients with endometrial malignancy who underwent either pelvic only or combined pelvic and para-aortic lymphadenectomy. Their results, published in 2010, found that more extensive lymphadenectomy improved survival in women with intermediate and high risk cancers, but not in women with low risk cancers[47]. Thus, SLN biopsy is likely only appropriate for women with early stage disease.

As previously described in the context of vulvar cancer, ultra-staging can provide added benefit when a select few nodes have been removed. Kim *et al*[48] report on 425 women who underwent SLN biopsy at the time of staging for low grade endometrial cancer. Ultra-staging was used when standard hematoxylin and eosin (H and E) staining did not identify metastatic disease, and the number of metastatic cancers diagnosed doubled with ultra-staging[48]. Others have also documented increased detection rates with ultra-staging[38,49]. The importance of these low-volume metastases should be underscored, as they are associated with worse outcomes and increased risk of recurrence[49,50]. However, the most appropriate management of these micrometastases remains unknown.

The low false negative rates and high sensitivity of sentinel nodal biopsy when done as part of a comprehensive algorithm make it a practical and appealing solution to the problem of staging women with early stage endometrial cancer. However, lymph node involvement is low for many women with early stage endometrial cancer and the survival benefit of adding SLN biopsy is unknown. At this time we feel SLN biopsy is investigational in women with endometrial cancer and should be done only on protocol. Routine pelvic and para-aortic lymphadenectomy should be performed on women at risk for lymph node metastasis. Additional information regarding long-term outcomes including overall survival among women undergoing SLN biopsy alone is still needed before we can determine which women will most benefit from the addition of a SLN biopsy and when we can omit pelvic and para-aortic lymphadenectomy.

CERVICAL CANCER

Despite not being an element of the FIGO clinical staging for cervical cancer, lymph node status is one of the most influential factors in disease free and overall survival for women with early stage disease[51]. The current standard of care for women with cervical cancer treated surgically includes bilateral pelvic lymphadenectomy plus or minus para-aortic lymphadenectomy. This

procedure however comes with significant morbidity, such as prolonged operative times, nerve and vascular injury, lymphocysts, and lymphedema[52]. However, only about 15% of women with early stage disease have lymph node metastases, meaning that the majority of the women are exposed to the increased morbidity of lymphadenectomy without an associated survival benefit[53]. This creates a prime opportunity for sentinel node biopsy.

There are a multitude of studies investigating the accuracy of sentinel node biopsy in cervical malignancy, and a recent systematic reviewed by Kadkhodayan and others analyzed the results of 67 such articles. They determined that the pooled detection rate of sentinel nodal mapping was 89.2% (95%CI: 86.3%-91.6%), with an overall sensitivity of 90% (95%CI: 88%-92%). When comparing the results of all included studies, they found that SLN detection rates were lower when using blue dye alone, and highest when the combination of blue dye and radiotracer. They determined that dilution of blue dye, superficial injections, and cervical injections were all associated with higher detection rates[54]. It has also been reported that SLN detection is best when done within 30 min of blue dye injection; when searching 50 min or greater after injection nodes are not able to be identified[55]. Others have found slightly improved detection rates when radiotracer is injected the day prior to nodal biopsy as compared to 2 d prior, although the difference is small and not statistically significant[56]. Furthermore, minimally invasive techniques (*via* either conventional or robotic laparoscopy) yield improved detection as compared to an open approach[54].

One important consideration in cervical cancer is the impact that positive lymph nodes have on indicated treatment. When lymph node metastases are detected during radical hysterectomy, para-aortic lymph node dissection is often performed and the remainder of the procedure is typically aborted, as the patient will subsequently require chemoradiation with the uterus and cervix *in situ*. Because of this, intraoperative detection of lymph node metastases is a very useful tool. Unfortunately the Kadkhodayan *et al*[54] review found that the pooled detection rate of lymph node disease with frozen section is low at 60%, a value which was influenced largely by the fact that frozen section analysis was not able to detect small macrometastatic and micrometastatic disease[54].

Cibula *et al*[53] examined the prognostic significance of low volume SLN disease in 645 women with early-stage cervical cancer who underwent SLN biopsy followed by complete pelvic lymphadenectomy. They found that isolated tumor cells were not independently associated with a decrease in overall or recurrence free survival. However, the presence of micrometastases was an independent prognostic factor for overall survival, and was equivalent to the survival effect of macrometastases. This serves to highlight the important role of ultra-staging in the management of these patients. Unfortunately, the most appropriate management for these isolated tumor cells remains unclear.

As cancer of the cervix is a midline disease, it must be assumed that tumors will drain to bilateral lymphatic basins. Failure of mapping on one side can be due to extensive tumor involvement on the un-mapped side, which in turn leads to significant false-negative rates with SLN detection. Cormier and others published an algorithm wherein all SLNs are removed, any suspicious nodes are removed whether they have mapped or not, and in the instance of only unilateral mapping contralateral pelvic nodal dissection and parametrectomy is done. They applied this method to a prospectively collected database of 122 patients who underwent SLN mapping followed by complete bilateral nodal dissection, and found that use of the algorithm would lead to detection of all cases of lymph node metastases, and avoid bilateral nodal dissection in 75% of cases[57]. Such an approach is likely the best way to optimize detection of metastatic disease while minimizing unnecessary complete nodal dissections.

Tumor size is also an important factor in the use of SLN biopsy in cervical cancer. When larger tumors are present there is a higher risk of replacement of lymph nodes with tumor, leading to decreased uptake of tracers. This can lead to either no identification of a sentinel node, or dye uptake by a non-sentinel node because of alterations in lymphatic drainage cause by tumor spread. Because of this a cutoff of SNL mapping only in tumors $\leqslant$ 2 cm or $\leqslant$ IB2 has been suggested[54].

To date, prospective studies on the survival outcomes of women who undergo SLN biopsy alone without concurrent pelvic lymphadenectomy are lacking. However, it is known that in a population of women with early stage disease those with positive lymph nodes do not see a survival advantage with more extensive lymphadenectomy. Conversely, women with negative lymph nodes do experience improved survival when a greater number of nodes are removed[58]. It is important to note that the study which reported those findings did not employ ultra-staging and it is possible that a portion of the "node negative" women who benefited from greater dissection would have in fact had micrometastatic disease detected with more advanced pathologic evaluation.

Based upon the above findings, SLN mapping in early stage cervical malignancy is a feasible and reliable approach for detecting metastatic disease. Given the morbidity of total pelvic lymph node dissection, and the relative infrequency with which metastatic disease is present in early cervical disease, SLN mapping has encouraging possibilities in select patients. However, larger prospective studies evaluating the long-term outcomes in patients who undergo SLN biopsy without subsequent complete lymphadenectomy are needed before clinical recommendations can be made.

CONCLUSION

SLN biopsy is a well-developed technique that is now

the standard of care in melanoma, breast cancer and penile cancer. In women with early vulvar cancer sentinel node biopsy should be considered a feasible alternative to total inguinal femoral lymphadenectomy. When undertaken by a qualified multidisciplinary team SLN biopsy is a safe approach that improves a woman's quality of life. In fact, SLN biopsy is the standard of care at some institutions for vulvar cancer patients.

In endometrial cancer, when using the appropriate technique lymphatic mapping demonstrates high sensitivity for detecting metastatic disease. While prospective studies applying these findings are ongoing, currently available data are promising that sentinel nodal detection may soon become widely accepted as an alternative standard of care for select cases of endometrial cancer.

In cervical cancer, sentinel node biopsy is practical for women with small lesions ($\leqslant$ 2 cm) and has the potential to spare a substantial proportion of women the morbidity of extensive nodal dissection. When used in conjunction with an algorithm which accounts for incomplete bilateral mapping the diagnostic yield is quiet high, however prospective data on survival and outcomes of women who undergo SLN biopsy are needed before it can be considered a viable alternative to complete lymphadenectomy.

While the process of ultra-staging lends additional information about the spread of disease, large-scale prospective data are needed in all three of these cancers to better understand the significance and proper treatment of micrometastatic malignancy.

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