Lymphatic Mapping and Sentinel Node Biopsy in Vulvar, Vaginal, and Cervical Cancers

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Over the past 15 years, lymphatic mapping and sentinel lymph node biopsy in vulvar, vaginal, and cervical cancers have been explored by gynecologic oncologists around the world. Based on the results of multiple single-institution studies, most in our field are optimistic that these techniques will increase the rates of detection of lymph node metastasis while decreasing the morbidity associated with lymphadenectomy. Large validation studies are currently underway in both the United States and Europe. In this review article, we present the published data on mapping techniques and discuss future considerations for these technologies.

In 1977, Cabanas reported his initial experience with lymphatic mapping and sentinel lymph node detection in men with penile cancer.[1] He hypothesized that tumors spread from the primary lesion to the draining nodal basins in an orderly, predictable pattern and that tumor emboli would not "skip" primary draining nodal basins for upper-echelon nodes. These initial draining basins were termed "sentinel nodes," as they were metaphorically the lookouts for all upper-echelon, or nonsentinel, nodes. A more modern and succinct definition of a sentinel lymph node is "any lymph node that receives lymphatic draining directly from a tumor site."[2]

Although the early pioneering studies in lymphatic mapping and sentinel lymph node biopsy were in patients with penile cancer, it was breast and melanoma surgeons who led the majority of the research in the 1980s and 1990s.[3,4] Currently, lymphatic mapping and sentinel lymph node biopsy, in lieu of complete regional lymphadenectomy, are the standard of care for breast cancers and melanomas. This technique has also been explored in other malignancies, including cancers of the head and neck, oropharynx, thyroid, stomach, colon, and bladder. In the past 15 years, lymphatic mapping has been explored in almost all of the gynecologic malignancies, including those of the vulva, vagina, cervix, and uterus.

A variety of technologies exist to help surgeons locate the sentinel nodes. Preoperative lymphoscintigraphy uses a radiolabeled colloid injected peritumorally to identify the sentinel node. A scanning machine detects the gamma emissions from the colloid (typically technetium-99) after it has drained to the sentinel lymph node. Gamma emissions from a radiolabeled colloid can also be followed intraoperatively using a handheld gamma probe to pinpoint the sentinel node. Patent blue dyes may also be injected peritumorally for visual identification of sentinel nodes during surgery. Resected sentinel nodes may therefore be "hot" (positive for the radiolabeled colloid), "blue" (positive for patent blue dye), or both hot and blue. Most studies of lymphatic mapping for breast cancer and melanoma have found that a combination of radiolabeled colloid and blue dye leads to higher sentinel node detection rates. This appears to hold true for the gynecologic malignancies, as will be discussed in this review.

The objective of this article is to review the current literature on lymphatic mapping and sentinel node detection in women with gynecologic malignancies. We will pay particular attention to the rationale for mapping, the reliability of the techniques, the localization of sentinel nodes, and the utility of pretherapeutic lymphoscintigraphy. Among studies of cervical and vulvar cancers, there are multiple case reports, small series (<20 patients), and large series (≥20 patients). We included only those series with more than 20 patients in our review, since a long-recognized limitation of lymphatic mapping is the higher rate of false-negative sentinel node detection in the first few cases a surgeon performs.[5,6] By restricting the eligible studies in this manner, we hoped to assure that the individual surgeons in each reported series would have obtained proficiency (ie, master the "learning curve") in sentinel lymph node mapping for gynecologic malignancies.

Vulvar Cancer

Epidemiology
An estimated 3,490 new cases of vulvar cancer were diagnosed in the United States in 2007, and an estimated 880 deaths resulted from the disease. Most vulvar cancers have squamous cell histologies (more than 90%), with melanoma accounting for the majority of the remaining tumors. For patients with clinical stage I squamous cell carcinoma of the vulva, the risk of lymph node metastasis is 10.7%. This risk increases to 26.2% for clinical stage II disease and to 64.2% for clinical stage III disease. The lymphatic drainage of the vulva is almost exclusively to the inguinofemoral triangle, which could be considered a sentinel lymph node basin. Although some anatomists have hypothesized that lymph drains directly from the vulva to the pelvis, this route has never been demonstrated clinically. Unilateral vulvar lesions, typically defined as tumors located more than 2 cm from the midline, primarily drain primarily to the ipsilateral groin nodes.

Unilateral and bilateral inguinofemoral lymphadenectomies have relatively high rates of postoperative complications, with as many as two-thirds of patients experiencing wound breakdown, lymphocyst formation, and/or lymphedema as a result of their groin dissection. For this reason, and because vulvar cancers have a highly predictable anatomic drainage pattern, lymphatic mapping and sentinel node dissection are seemingly ideal for this disease site.

### Success of Lymphatic Mapping

#### Table 1

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<th>Summary of Published Literature on Lymphatic Mapping in Patients With Vulvar Cancer</th>
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Multiple investigators have published their experiences with lymphatic mapping and sentinel node biopsy in women with vulvar cancer. [Table 1](#) lists case series in the English-language literature that included more than 20 patients in whom sentinel node biopsy was followed by complete inguinofemoral lymphadenectomy and that provided enough data to calculate the sensitivity, false-negative rate, and negative predictive value of sentinel node biopsy.

At least one sentinel node was identified in 97% of the patients reported. However, a sentinel node was identified in only 84% of groins explored. This is likely a result of the standard practice of dissecting groins bilaterally for vulvar lesions less than 2 cm from the midline. Many of these lesions will have only ipsilateral lymphatic drainage, so the contralateral groin will not contain a sentinel node.

For the combined group—the 383 patients in the 10 series included in Table 1—the overall sensitivity of sentinel node biopsy was 97.6%, with a false-negative rate of 2.4%. Only three patients had a truly false-negative sentinel node result—ie, the sentinel node was negative but metastatic disease was present in other nodes. Another five patients (1.3%) had metastatic disease in the groin, but no sentinel node was identified. Whether these five cases should be considered false-negatives or technique failures is debatable. One reason that lymphatic mapping might not be successful in identifying the sentinel node is that when the node is completely replaced with tumor, radiolabeled tracers and/or blue dye cannot enter the tissue as readily. Most would argue that in the absence of identification of a sentinel node in a draining groin, a complete inguinofemoral lymphadenectomy should be performed.

Early experiences using only blue dye resulted in a low identification rate, with sentinel nodes identified upon visual inspection in only 64% of groins dissected (Table 1). Since these blue-dye-only studies were among the earliest in vulvar cancer, the low detection rate may indicate that investigators were on the early portion of the learning curve and did not have the benefit of the knowledge accumulated by the research community since then. Another reason for the low detection rate may have been the lack of a radiolabeled tracer as part of the technique. Once radiolabeled colloids were added, sentinel node identification rates increased dramatically. Overall, the detection rate per groin is 91% for intraoperative mapping using a radiolabeled colloid combined with blue dye. For preoperative lymphoscintigraphy and intraoperative mapping using a
radiolabeled colloid only, the rate is 92%, and for preoperative lymphoscintigraphy and intraoperative mapping using a radiolabeled colloid combined with blue dye, the rate is 90% (Table 1).

As shown in Table 1, even the largest validation studies for this technique are relatively small. Currently in the United States, the Gynecologic Oncology Group (GOG) is prospectively evaluating the sensitivity, false-negative rate, and negative predictive value of lymphatic mapping and sentinel lymph node dissection in a multi-institutional study (GOG 173). The goal is to complete patient accrual in 2008.

Gynecologic oncologists in Europe recently reported their data from the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V).[20] In contrast to the validation study underway by the GOG, the GROINSS-V study is an observational study in which the investigators performed sentinel node–only biopsies instead of complete inguinofemoral lymphadenectomy in women with squamous cell carcinomas of the vulva ≤ 4 cm in size. At a median follow-up of 35 months, they observed 6 groin recurrences (2.3%) in 259 women with unifocal vulvar disease who had negative sentinel node biopsies. Interestingly, this reported recurrence rate of 2.3% is almost identical to the false-negative rate of 2.4% shown for the combined studies in Table 1.

Other smaller studies have also reported their experience with sentinel node–only biopsy in lieu of complete lymphadenectomy in women with vulvar cancer. Vidal-Sicart and colleagues[21] reported a prospective study of 70 patients with vulvar cancer who underwent lymphatic mapping and sentinel node biopsy. The first 50 patients were considered the validation group, in which lymphatic mapping and sentinel node biopsy were followed by complete inguinofemoral lymphadenectomy. The next cohort of 20 women was the application group, in which only sentinel node biopsy was performed. In 7 of these 20 patients, metastatic disease was found in the sentinel lymph node; complete lymphadenectomy followed by adjuvant chemotherapy and/or radiation was then performed in six women. In the seventh, only isolated tumor cells were found in the sentinel lymph nodes, so adjuvant radiation therapy was administered without reexploration of the groin. The remaining 13 patients without disease in their sentinel nodes were assigned to close observation.

At a median follow-up of 10 months, no groin recurrences had been observed in these women. After publication of the manuscript, however, and 12 months after surgery, one patient with a negative sentinel lymph node biopsy had a recurrence in the same inguinofemoral basin in which the sentinel node was identified. She underwent complete lymphadenectomy and, at the time of this writing, has no evidence of disease (personal communication, Vidal-Sicart).

A similar experience with sentinel node biopsy for T1 squamous cell carcinomas of the vulva was reported by Terada et al.[22] Of the 21 patients who underwent sentinel lymph node biopsy only, 3 had metastatic disease in the sentinel nodes. At a median follow-up of 4.6 years, none of the 18 patients with a negative sentinel node biopsy had had a groin recurrence, although 2 had local recurrence on the vulva.

Anatomic Location of Sentinel Nodes

As previously stated, no study has reported direct drainage of lymph from the vulva to the pelvis. The location of the sentinel node within the inguinofemoral triangle, however, varies greatly. Our group previously suggested that groin recurrence in women with no sentinel node identified and a negative lymphadenectomy specimen may be associated with insufficient dissection of the groin, most likely with nodal tissue left in the medial part of the inguinofemoral triangle.[23] Locating the sentinel node (the most likely site of metastatic disease) is of the utmost importance.

Rob et al[17] published the most detailed study about sentinel node location in vulvar cancer. They divided the lymph nodes of the groin into four regions: the superficial medial group (Sf-M), located above and medial to the femoral vein and medial to the saphenous vein; the superficial intermediate group (Sf-IM), located in the vicinity of but superior and lateral to the saphenous and femoral veins; the superficial lateral group (Sf-L), located in the outer third of the groin; and the profundum nodes group (Pf), located deep, medially along the femoral vein. Of the 118 sentinel lymph nodes found in 82 groins in this study, 58 (49%) were in the Sf-M region, 41 (35%) were in the Sf-IM region, and 19 (16%) were located in the Pf region. No sentinel lymph nodes were found in the Sf-L region. These data are important for anyone who performs groin dissections, even those who do not perform lymphatic mapping.

Utility of Pretherapeutic Lymphoscintigraphy

It is not certain whether preoperative lymphoscintigraphy for the detection of sentinel nodes in vulvar cancer is necessary. Multiple arguments exist for not performing the procedure. First,
consistent drainage of primary vulvar lesions to the inguinofemoral triangle suggests that the scan might add little to surgical planning. This is in contrast to, for example, cutaneous melanoma of the trunk, for which lymphatic drainage is unpredictable and the surgical approach changes according to the lymphoscintigraphy findings. Another argument against routine use of lymphoscintigraphy is the added cost, time, and patient discomfort involved. Patients are required to visit the nuclear medicine clinic hours or days before the surgical procedure and undergo injection with the radiolabeled colloid around the vulvar lesion, without an analgesic.

For well-lateralized lesions (for which only unilateral groin dissection is planned) and for lesions crossing the midline (for which bilateral groin dissections are indicated), preoperative lymphoscintigraphy probably is unnecessary. However, it may be useful for lesions near the midline for which bilateral sentinel lymph nodes in only 6 (46%) of 13 patients with lesions "close to midline," as opposed to in 13 (93%) of 14 patients with lesions abutting or crossing the midline. For 12 (92%) of those 13 women with lesions "close to midline"—defined as a location less than 1 cm from but not touching the midline—sentinel lymph nodes were found only in the ipsilateral groin. Perhaps preoperative lymphoscintigraphy could have identified some women with lesions "close to midline" at low risk for bilateral drainage who could have safely undergone ipsilateral groin dissection only. However, one must be cautious in abandoning standard-of-care bilateral groin dissections for lesions near the midline based on lymphoscintigraphy results only. Louis-Sylvestre and colleagues[24] found that in 13 patients who had lesions less than 1 cm from the midline and in whom lymphoscintigraphy identified unilateral drainage only, 3 had metastatic disease in nodes located in the contralateral, lymphoscintigraphy-negative groin.

Vaginal Cancer

Epidemiology

There were an estimated 2,140 new cases of vaginal cancer in the United States in 2007, and 790 vaginal cancer–related deaths.[7] This rare cancer accounts for only 1% to 2% of gynecologic malignancies. As in vulvar cancer, the vast majority of vaginal cancers are squamous cell carcinomas; a small percentage are melanomas, clear cell carcinomas, and adenocarcinomas. Unfortunately, more than 80% of vaginal cancers have metastasized by the time of diagnosis. Radiation therapy is the preferred treatment for most cases of vaginal cancer due to its excellent tumor control and good functional results. Surgery is occasionally performed in cases of radiation therapy failure, nonepithelial tumors (eg, melanoma), and stage I clear cell cancer in young women.[25]

Success of Lymphatic Mapping

Few studies have been done on lymphatic mapping for vaginal cancer since it is so rare. To date, only six cases of lymphatic mapping for patients with primary vaginal cancer have been reported in the English-language literature.[26-29] In five of those six cases, at least one sentinel node was identified (four patients with melanoma and one with adenocarcinoma). In the lone patient with squamous cell carcinoma, a sentinel node was not identified. We recently submitted for publication our experience with lymphatic mapping in 14 women with vaginal cancer.[30] In our series, at least one sentinel node was identified in 11 (79%) of the 14 women. However, calculating the sensitivity, false-negative rate, and negative predictive value would not be appropriate given the small numbers. Because the majority of women with vaginal cancer will receive definitive radiotherapy and will not undergo lymphadenectomy, validation of lymphatic mapping and sentinel node biopsy is likely impossible.

Anatomic Location of Sentinel Nodes

Lymphatic drainage of the vagina has never been well defined. Most believe that tumors in the upper vagina drain via the lymphatic system of the cervix to the pelvic and para-aortic nodes and that cancers in the lower vagina drain via the vulvar lymphatic channels to the inguinofemoral triangle. In addition, some anatomists have hypothesized that lymphatic channels in some parts of the anterior vaginal wall may drain directly into the pelvic nodes.[29] The uncertainty about the exact nature of lymphatic drainage of the vagina is due not only to the complexity of the routes but also to the fact
that most of the studies mapping this lymphatic drainage date were done before 1970, when mapping techniques were more primitive.

More recent lymphatic mapping studies of the vagina have called into question the traditional thinking on routes of drainage. In our study,[30] three (50%) of the six vaginal cancers located in the lower third of the vagina, or introitus, drained directly to the pelvis, while two (50%) of the four tumors located at the apex of the vagina drained into the inguinofemoral triangle. There were no predictable drainage patterns for tumors of particular histologic type or tumors located anteriorly, posteriorly, or circumferentially in the vagina. We believe that long-held anatomic assumptions regarding the lymphatic drainage of the vagina should be reevaluated.

**Utility of Pretherapeutic Lymphoscintigraphy**

Owing to the ambiguous nature of the lymphatic drainage of the vagina, lymphoscintigraphy is an ideal modality to detect sentinel nodes in patients with vaginal cancer. For patients undergoing primary radiotherapy, identification of sentinel lymph nodes could guide clinicians to either shrink or expand the radiation field to incorporate suspicious nodes. In our study of lymphatic mapping for vaginal cancer, nine women were treated with primary radiation therapy, and three (33%) of them had their radiation field altered as a result of pretherapeutic lymphoscintigraphy.[30] For patients undergoing surgical resection of vaginal cancer, preoperative identification of sentinel nodes could direct the surgeon to perform dissections in the groin, the pelvis, or both.

Unfortunately, prospective studies to validate the use of lymphatic mapping in vaginal cancer will accrue slowly owing to the rarity of the disease, so treatment decisions will likely be based on small case series such as ours.

**Cervical Cancer**

**Epidemiology**

There were an estimated 11,150 new cases of cervical cancer in the United States in 2007, and approximately 3,670 women died of the disease.[7] More than half of women with cervical cancer are diagnosed with clinical stage I disease (ie, tumor clinically limited to the cervix) and thus are potential candidates for radical hysterectomy and pelvic lymphadenectomy.[31]

Patients with cervical cancer are seemingly excellent candidates for lymphatic mapping and sentinel node biopsy. First, a complete pelvic lymphadenectomy leads to lymphocyst formation in up to 20% of patients, and another 15% of women experience lymphedema.[32] Both of these complications can be avoided through successful sentinel node detection, which may prevent the need for a complete lymphadenectomy. Second, the cervix is a midline structure with a complex lymphatic drainage system and is easily accessible for injection with mapping compounds. Third, the lymph node status in women with cervical cancer is the most important prognostic factor and a major determinant in deciding whether to administer postoperative radiation therapy after radical hysterectomy. Fourth, sentinel node biopsy complements well the increasing interest in minimally invasive approaches for radical hysterectomy, since it may enable avoidance of a complete lymphadenectomy.[33]

In women with stage I disease, the risk of pelvic lymph node metastasis is 15% to 20%,[8] but sentinel lymph node biopsy can benefit patients with or without lymph node spread. For the majority of patients with disease confined to the cervix, radical hysterectomy and sentinel node biopsy could offer a good prognosis with surgery alone while presumably reducing the incidence of lymphedema and lymphocyst formation. For patients with metastatic disease in the lymph nodes, sentinel lymph node biopsy could allow surgeons to determine the presence and location of metastasis and thus limit the extent of dissection in the peritoneal cavity. Also, since postoperative adjuvant radiation therapy after exploratory surgery and complete lymph node dissection increases the risk of complications such as bowel obstruction/perforation and lymphedema,[34] sentinel node biopsy could be used to identify patients who need adjuvant therapy without performing complete lymphadenectomies and thus reduce complications from radiation therapy.

**Success of Lymphatic Mapping**

**TABLE 2**
Summary of Published Literature on Lymphatic Mapping in Patients
With Cervical Cancer

Multiple investigators have published their experiences with lymphatic mapping and sentinel node biopsy in women with cervical cancer.[35-54] Table 2 lists series in the English-language literature that included more than 20 patients in whom sentinel node biopsy was followed by complete pelvic lymphadenectomy (with or without para-aortic node dissection) and that provided enough data to calculate the sensitivity, false-negative rate, and negative predictive value of sentinel node biopsy. Studies of women who received preoperative chemotherapy or preoperative radiation therapy were excluded from Table 2, as it is not known how these preoperative treatments affect lymphatic mapping.

At least one sentinel node was identified in 89% of the cases reported. Detection rates improved as radiolabeled colloids were employed in addition to or instead of blue dye. Intraoperative lymphatic mapping with a blue dye alone identified a sentinel node in only 84% of patients, while intraoperative lymphatic mapping with a blue dye and a radiolabeled colloid identified a sentinel node in 96% of patients. Interestingly, in the combined analysis, the triple technique of preoperative lymphoscintigraphy and intraoperative lymphatic mapping using both a radiolabeled colloid and blue dye revealed a sentinel node only 91% of the time (as the triple technique would presumably be most effective).

The results from the combined studies shown in Table 2 were mirrored in individual studies. Malur et al[44] used only intraoperative lymphatic mapping with a radiolabeled colloid in their first 21 patients and located a sentinel node in 16 (76%). In the next 20 patients, they used both a radiolabeled colloid and blue dye intraoperatively and were able to find a sentinel node in 18 (90%). Similarly, Rob and colleagues[50] were able to locate a sentinel node in 83% of patients with intraoperative mapping using blue dye only, while intraoperative mapping with the combination of blue dye and a radiolabeled colloid increased the identification rate to 94%. Although a large part of the increase in detection rate is likely due to the combination of blue dye and a radiolabeled colloid, some can probably be attributed to improved identification in later cases as investigators mastered the techniques.

Ideally, lymphatic mapping and sentinel node biopsy should be performed in patients with early-stage disease, as lymphatic channels are more likely to be obstructed with metastases or inflammation-causing debris in patients with larger tumors. Coutant et al[55] found the sentinel node detection rate was 91% for early-stage cervical cancer but only 79% for advanced disease. Similarly, Rob and colleagues[56] found that the sentinel node detection rate decreased as the size of the primary lesion increased.

For the combined group—the 802 patients in the 20 series included in Table 2—the sensitivity of sentinel node biopsy was 93.2%, with a false-negative rate of 6.8%. In this group, only 11 patients had a truly false-negative sentinel node dissection.[37,39,42,49,51,53,54] The negative predictive value in the combined studies was 97.8%. Bilateral sentinel lymph nodes were found in only 65% of patients (12 of the 20 studies reported these data). This is surprising, as the cervix is a midline structure presumably with bilateral lymphatic drainage. The low rate of detection of bilateral sentinel nodes may be due to injection technique or alterations in the drainage of the cervix from prior obstetric trauma, pelvic inflammatory disease, or endometriosis. Many investigators suggest that, as in cases of unilateral drainage from a midline vulvar cancer, complete lymphadenectomies should be performed in the hemipelvis when a sentinel node is not found.

The Gynecologic Oncology Group is studying the utility of lymphatic mapping and sentinel lymph node biopsy in a multi-institutional trial (GOG 206). This study is designed to determine the sensitivity, false-negative rate, and negative predictive value of sentinel lymph node biopsies in women with early-stage cervical cancer.

Anatomic Location of Sentinel Nodes

Several authors have specifically investigated the locations of sentinel nodes in women with cervical cancer. Marnitz and colleagues[57] published an extensive analysis of sentinel node location. In that
study, 91% of sentinel nodes were found in the pelvis, with 71% of sentinel nodes found medial to the external iliac vessels along the external iliac vein and in the obturator space. Another 5% of sentinel lymph nodes were found along the common iliac vessels and in the presacral space, and 4% were found above the bifurcation of the aorta. A study by Bader et al[58] also reported that 91% of the sentinel lymph nodes were found in the pelvis. However, a large percentage of these sentinel nodes (43%) were found along the external iliac vessels, with only 26% found in the obturator space. Both studies reported sentinel nodes along the aorta less than 4% of the time, but other authors have reported metastatic disease in para-aortic sentinel nodes.[41,44,59]

The rate of sentinel node detection in the parametrium varies widely and has been reported as 3% to 21%.[56-58] The exact role of parametrial lymph nodes as sentinel nodes in women with cervical cancer is unclear. It makes sense that parametrial nodes ought to be sentinel in all patients with cervical cancer due to their anatomic location. However, this has yet to be proven. Intraoperative identification with blue dye and/or radiolabeled colloids in the parametrial nodes has proven difficult, as the blue dye passes through these nodes quickly, and their proximity to the cervix makes separate detection of a gamma-emitting radiolabeled colloid in these nodes difficult.

Utility of Pretherapeutic Lymphoscintigraphy

A majority of the large series, including our own, used preoperative lymphoscintigraphy for lymphatic mapping in patients with cervical cancer. In a previous review of our experience with this technology,[59] we found a poor correlation between preoperative lymphoscintigraphy findings and intraoperative mapping findings. For example, 71% of women with a single sentinel node identified during preoperative lymphoscintigraphy actually had multiple sentinel nodes discovered intraoperatively. More than half the patients with unilateral sentinel nodes found during preoperative lymphoscintigraphy had bilateral sentinel nodes found intraoperatively. Most important, among the nine patients (18%) who had metastatic disease found in a sentinel node on final pathology, no sentinel nodes were found with preoperative lymphoscintigraphy alone. In addition, among women who had sentinel nodes identified during preoperative lymphoscintigraphy but not intraoperatively, no metastatic disease was found in the resected nodes.

These data suggest that the addition of preoperative lymphoscintigraphy to lymphatic mapping in patients with cervical cancer contributes little to care. For this reason, the Gynecologic Oncology Group amended its mapping protocol to make this costly and uncomfortable test optional.

Future Directions

Some aspects of lymphatic mapping and sentinel node dissection need clarification in the coming years. First, we need to know how well the technique will work when extended beyond the few academic centers that are currently exploring its use. There is a steep learning curve for proper application of these techniques. Some have suggested that surgeons may need to perform as many as 60 procedures before being considered proficient with the mapping techniques in treating breast cancer.[6] For even the most active gynecologic oncologists, this is probably an unattainable goal, considering the relatively low incidences of these cancers. We believe 10 procedures is likely appropriate to familiarize oneself with and master these techniques.

Second, the scientific community needs to determine an acceptable false-negative rate for these techniques. Women with breast tumors larger than 1 cm routinely receive some form of adjuvant therapy, regardless of node status, which makes the accepted false-negative rate of 5% to 10% for breast cancer sentinel nodes reasonable. But for gynecologic malignancies of the lower genital tract, the decision about whether to give adjuvant therapy is often based solely on nodal status. In addition, recurrence in the nodal basins in women with vulvar, vaginal, and cervical cancers carries an extremely poor prognosis. Therefore, 10% is probably too high to be an acceptable false-negative rate for these procedures in gynecologic cancers.

Finally, what should be the decision regarding adjuvant therapy in women with micrometastatic disease (tumor metastasis smaller than 2 mm) found in the sentinel node? One of the major advantages of sentinel node biopsy is that it allows for closer pathologic examination of resected nodes with ultrastaging and immunohistochemical staining or even polymerase chain reaction-based testing. This additional pathologic scrutiny leads to increased detection of smaller and smaller tumor emboli. In cutaneous melanoma and breast cancer, sentinel lymph node status and the amount of tumor in the sentinel node have been formally adopted into the staging systems.[60,61] However, the clinical significance of these findings in gynecologic malignancies remains unknown.
Conclusions

The individual trials published to date are promising for the adoption of lymphatic mapping and sentinel node biopsy for malignancies of the lower genital tract. We believe the results from the GOG 173 study and the pending publication of the GROINSS-V study will likely support changing sentinel node biopsy from investigational to standard of care in the treatment of vulvar cancer. For cervical cancer, the GOG 206 study will hopefully corroborate the findings of smaller, single-institution studies and move the field toward a large, prospective validation study. As for lymphatic mapping and sentinel node biopsy for vaginal cancer, we are pessimistic that large studies are possible owing to the rarity of the disease. However, we do believe that pretherapeutic lymphoscintigraphy is a sensible option in the planning of treatment for patients with vaginal cancer.

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