Sentinel Lymph Node Mapping for Endometrial Cancer: A Modern Approach to Surgical Staging

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Abstract
Most patients with endometrial cancer will present with early-stage disease. Although the rate of metastasis in these patients is low, providing excellent prognoses, the standard of treatment in many practices still includes a complete or selective pelvic and para-aortic lymphadenectomy for staging; and accurate surgical staging is the most important prognostic factor. Many patients will undergo a comprehensive lymphadenectomy despite having disease confined to the uterus, resulting in prolonged operating time, additional cost, and potential side effects, such as lower extremity lymphedema. However, recent studies show that a complete lymphadenectomy may have no therapeutic benefit in patients with early-stage endometrial cancer.

Sentinel lymph node (SLN) mapping, which has been used in other cancer types, may be an acceptable surgical strategy between a complete lymphadenectomy and no nodal evaluation in patients with endometrial cancer. SLN mapping is based on the concept that lymph node metastasis is the result of an orderly process; that is, lymph drains in a specific pattern away from the tumor, and therefore, if the SLN, or first node, is negative for metastasis, then the nodes after the SLN should also be negative. This approach can help patients avoid the side effects associated with a complete lymphadenectomy, although disease must be thoroughly staged for accurate prognosis and determination of appropriate treatment approach. Surgeon experience, adherence to an SLN algorithm, and the use of pathologic “ultrastaging” are key factors for successful SLN mapping. (J Natl Compr Canc Netw 2014;12:288–297)

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Learning Objectives
Upon completion of this activity, participants will be able to:
- Define the key factors for successful SLN mapping including adherence to an SLN algorithm and use of “ultrastaging”
- Compare and contrast the surgical strategies of SLN mapping, complete or selective lymphadenectomy, or no nodal evaluation in patients with endometrial cancer
- Define the key factors for successful SLN mapping including adherence to an SLN algorithm and use of “ultrastaging”

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Sentinel lymph node (SLN) mapping is an image-guided procedure that is well established in the treatment of cancers, such as melanoma and breast cancer. This approach is based on the concept that lymph drains in an orderly pattern away from the tumor through the lymphatic system; therefore, if the SLN, or first node, is negative for metastasis, then the ensuing nodes should also be negative. A recent study showed that SLNs are 3 times more likely than non-SLNs to harbor metastatic disease. Gould et al coined the term sentinel node in 1960 with his observations of carcinoma of the parotid gland. He suggested that examining the SLN for metastatic disease could help determine whether a patient needed a radical neck dissection. His approach was based on simply identifying the anatomic location of the SLN. In 1977, Cabanas described the SLN in patients with penile carcinoma, this time with the use of the imaging procedure lymphography. SLN mapping in endometrial cancer was introduced by Burke et al in 1996, but has only recently gained popularity. The appeal of SLN mapping lies in the possible avoidance of “overstaging” via lymph node dissection of normal/negative nodes and enhanced precision in finding micro-metastasis with pathologic ultrastaging of SLNs. Comprehensive lymphadenectomy may be associated with detrimental side effects, such as lower extremity lymphedema and lymphocysts, which can negatively impact quality of life. It is also likely associated with greater operating time, prolonged anesthesia, increased blood loss, vascular and nerve injury, and an increased conversion rate from laparoscopy to laparotomy to complete the operation successfully. However, because accurate surgical staging is the most important prognostic factor, the standard in many practices continues to include a comprehensive lymphadenectomy. Furthermore, no prospective randomized trials have yet assessed the efficacy of SLN mapping procedures in endometrial cancer, and no long-term survival data are currently available.

The Importance of Lymph Node Assessment

Endometrial cancer is the most common gynecologic malignancy; an estimated 44,560 women will be diagnosed with the disease in the United States in 2013. Most of these women will present with early-stage disease (90%), without metastasis, limiting the amount of deaths to approximately 8190 per year. Because most of these tumors will be confined to the uterus (International Federation of Gynecology and Obstetrics [FIGO] stage I), the 5-year overall survival rate in this patient population is 80% to 90%. Approximately 10% to 15% of these patients will, in fact, have metastatic nodal disease, and nearly 15% will be deemed to have grade 1 tumors preoperatively on office biopsy or dilatation and curettage will actually have higher-grade disease on final pathologic review after hysterectomy, therefore, it is of utmost importance to stage and treat these patients properly and avoid missing undetected metastatic disease that may upstage the patient.

Most patients with endometrial cancer will undergo initial surgical treatment that will include a total hysterectomy, bilateral salpingo-oophorectomy, and pelvic washings. Although the rate of metastasis in this patient population is low, the standard of treatment also includes a complete or selective pelvic and para-aortic lymphadenectomy for staging disease. Proper surgical staging, the most important prognostic factor, provides information on the actual extent of disease rather than on perceived risks based on uterine factors, such as grade, histology, and depth of myometrial invasion, which helps tailor adjuvant therapy.

Unfortunately, many patients with early-stage endometrial cancer will undergo surgery with insufficient nodal evaluation, with their nodes being palpated, biopsied only if enlarged, or completely ignored. Studies have shown rates of nodal assessment as low as 30%, although that percentage has increased as the importance of nodal assessment has been realized. When surgical staging is inadequately performed, patients can be subjected to unnecessary adjuvant therapy, such as pelvic radiation therapy and its associated side effects. Based on the current standard of treatment, surgeons are faced with the dilemma of “understaging” versus “overtreating.” Traditionally, it has been suggested that the more nodes removed, the better the chance of detecting metastasis, but also the more likely the patient will develop side effects. The use of SLN mapping in patients with endometrial cancer may be an acceptable solution, providing a middle ground between the polarized schools of thought: complete lymph-
focused Review
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Adequate staging. A potential pitfall to SLN mapping is that some, but possibly not all, positive lymph nodes may be removed, leaving the question: does every microscopically positive node need to be removed to stage patients? And is there a potential therapeutic role of removing normal-appearing lymph nodes?

The Road to SLN Mapping in Endometrial Cancer

In current practice, the importance of lymph node assessment for proper surgical staging in this patient population cannot be stressed enough, although lymph node removal may increase operative time and blood loss, and is associated with vascular injury, lower extremity lymphedema, and lymphocyst formation. In a study of 1289 patients with uterine corpus malignancies at Memorial Sloan-Kettering Cancer Center, 16 (3.4%) of 469 patients who had 10 or more lymph nodes removed at surgery developed new postoperative symptomatic leg lymphedema. Furthermore, 2 large recently reported trials have questioned the survival benefit of a comprehensive lymphadenectomy in this disease. One such study, A Study in the Treatment of Endometrial Cancer (ASTEC), was a randomized multicenter study of more than 1400 patients, which showed no therapeutic benefit to lymphadenectomy in early-stage endometrial cancer; however, almost half of the patients randomized to the lymph node dissection arm had 9 or fewer nodes removed (ie, possible inadequate staging via a non-SLN approach). The ASTEC trial was also criticized because many patients were treated with postoperative radiation regardless of the status of their lymph nodes. In a randomized trial by Panici et al that required a minimum of 20 lymph nodes removed per patient, no difference was seen in overall survival. The findings of these studies, however, contradicted earlier retrospective studies, such as that of Kilgore et al in 1995, which reported a significant survival advantage for patients with endometrial adenocarcinoma undergoing multiple-site pelvic lymph node sampling versus no node sampling, suggesting a therapeutic benefit to lymphadenectomy. More recently, the retrospective study on Survival Effect of Para-Aortic Lymphadenectomy (SEPAL) in endometrial cancer showed that overall survival was significantly improved in select intermediate- and high-risk patients undergoing pelvic and para-aortic lymph node dissection. However, the median number of nodes removed was much larger than in most studies, and it was also difficult to determine whether the improvement in overall survival was a result of the removal of the para-aortic nodes or of the adjuvant chemotherapy.

In a pilot study of 42 patients with grade 1 endometrioid endometrial cancer, the most common anatomic sites where SLNs were identified were the internal iliac, 52 (36%); external iliac, 43 (30%); obturator, 34 (23%); and common iliac regions, 11 (8%); these are the areas involved in a pelvic nodal dissection (Figures 1 and 2). Only 5 cases (3%) had para-aortic SLN involvement. The para-aortic nodal dissection may be an area of possible overstaging, which would be limited with successful negative bilateral pelvic SLN map-
In a 2009 study, 847 (44%) of 1942 patients had both pelvic and para-aortic nodes removed during initial surgery. Only 12 (1.6%) of 734 patients who had negative pelvic nodes had isolated positive para-aortic nodes. When 8 or more negative pelvic nodes were removed, which is a number some consider adequate for accurate pelvic node dissection and staging, only 7 of 640 patients (1%) had isolated para-aortic nodal metastasis. In a study of 1920 patients (all had ≥ 1 node removed) using Classification and Regression Tree (CART) analysis, Barlin et al reported no association with the para-aortic nodal assessment and overall survival (P=.450). They also showed that stage I versus stages II–IV and grades 1–2 versus grade 3 (a binary grading system of low- vs high-grade) were predictors of overall survival. In other words, what seems to be important as far as staging is the proper determination of uterine fundus–contained disease versus disease outside the uterine fundus, and the pathologist determining the grade of the tumor as low- versus high-grade (grade 1–2 endometrioid is considered low-grade, and grade 3 endometrioid or serous, clear cell, or carcinosarcoma is considered high-grade).

Even pelvic lymph nodes, which are more likely to contain metastatic disease, may sometimes be unnecessarily removed (overstaged). For example, the “circumflex iliac” lymph nodes are often removed during a routine bilateral pelvic lymphadenectomy, and these nodes are often benign, especially when other nodal areas are also negative. Removing these nodes may cause lymphatic obstruction to the lower extremity, lower abdominal wall, and pubic region, increasing the risk of lymphedema.

### SLN Mapping Techniques

A radioactive tracer and colored dye (often blue or green) are used to locate “hot” nodes or visualize colored nodes. SLNs are considered positive if they contain macrometastasis (tumor clusters >2 mm), micrometastasis (tumor clusters 0.2–2.0 mm), or isolated tumor cells (single tumor cells or tumor clusters ≤0.2 mm). The treatment of women with only isolated tumor cells in SLNs is still a subject of much current research. SLNs containing only isolated cytokeratin-positive “cells” should be considered negative for metastasis.

Three different types of SLN mapping techniques exist based on site of injection: 1) uterine subserosal, 2) cervical (Figure 3), and 3) endometrial via hysteroscopy. The author’s group prefers a cervical injection, although others have argued that a peritumoral injection, either hysteroscopic or fundal, is more appropriate. Their rationale for using a cervical injection includes the following: 1) the main lymphatic drainage to the uterus is from the parametria; therefore, a combined superficial (1–3 mm) and deep (1–2 cm) cervical injection is adequate; 2) the cervix is easily accessible; 3) the cervix in women with endometrial cancer is rarely distorted by anatomical variations, such as myomas, which sometimes

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**Figure 2** The less common locations of sentinel lymph nodes, usually seen when lymphatic trunks do not cross over the umbilical ligament but follow the mesoureter cephalad to the common iliac and presacral sentinel lymph nodes.


**Figure 3** Three different options for direct cervical injection: a 2-sided option (A) and the 4-quadrant options (B and C).

make uterine serosal mapping impossible; 4) the cervix in women with endometrial cancer is rarely scarred from prior procedures, such as conization or bulky tumor infiltration; and 5) a uterine fundal serosa mapping does not reflect the parametrial lymphatic drainage of the uterus (the main route of drainage), and most early-stage endometrial cancers do not have disease infiltrating and ulcerating the uterine fundal serosa.26 The main argument against the cervical injection is that it has a lower para-aortic detection rate, as opposed to the hysteroscopic approach; but as previously mentioned, when the pelvic lymph nodes are negative for metastasis, disease is unlikely to be found in the para-aortic nodes,21 and to date, no definitive well-documented association exists between para-aortic nodal assessment and improved overall survival.13 In a recent large meta-analysis, Kang et al27 reported a decrease in detection rates when the cervical method was not used, although without statistical significance. These investigators also recommended that the “subserosal injection-only” technique be avoided because of decreased sensitivity. For these reasons and based on the authors’ experience and that of other investigators, they prefer the cervical-only approach and describe the procedure herein.

**Lymphoscintigraphy**

A radiolabeled colloid, usually technetium-99 (99mTc), is injected into the cervix the day of or the day before surgery. The 99mTc is then carried via lymph through the lymphatic capillaries to the SLNs. In the “short” protocol (day of surgery), 0.2 to 1.0 mCi of the 99mTc is injected. In the “long” protocol (20–24 hours before surgery), an additional 2.0 to 4.0 mCi of colloid is used. A preoperative planar lymphoscintigram is taken 20 to 30 minutes after injection for a short protocol, and immediate “dynamic” images and subsequent “static” images are taken to locate the nodes. Gamma probes, such as a laparoscopic SLN probe or a handheld open-procedure SLN probe, are used to detect the hot nodes. Single-photon emission computed tomography (SPECT), which uses 3-dimensional localization of hot nodes also detected through a gamma probe, can be used.28

**Colored Dye Injection:** The colored dye (isosulfan blue 1, methylene blue 1%, or patent blue 2.5% sodium) is injected while the patient is under anesthesia in the operating room. The dye is injected the same way as the radiotracer. A spinal needle or Potocky-type needle is used to inject 4 mL of dye into the cervical submucosa and stroma. The 4 mL can be divided into 4 separate injections, 1 into each quadrant of the cervix (1 mL each). The injections also can be given at the 3 and 9 o’clock positions (Figure 3), which correspond to the parametria and will keep the bladder flap from being stained, which is seen with the
12 o’clock injection. The dye should be injected slowly, at a rate of 5 to 10 seconds per quadrant. Complications with blue dye are rare, consisting mostly of allergic reactions, including swelling and pruritis of the hands, feet, abdomen, and neck. Severe reactions include edema of the face and glottis, respiratory distress, and shock. Blue dye will also turn the urine blue-green for up to 24 hours.

**Fluorescent SLN Imaging With Indocyanine Green**

Indocyanine green (ICG), using near-infrared fluorescence imaging, has recently emerged as an excellent dye for SLN mapping (Figures 4, 5, and 6). The 25-mg dry powder bottle is mixed with 20 mL of sterile water in the operating room, and 2 to 4 mL is injected directly into the cervix in similar fashion to that of blue dye. The main contraindication is iodine allergy, which the current US-available product contains. The SLN detection rates with ICG and the bilateral SLN detection rates appear comparable or better than those of blue dye only or radiocolloid. Fluorescent SLN localization with ICG is currently the preferred mapping approach at the authors’ institution.

**Pathology**

A key component of the added value of SLN procedures in endometrial cancer is enhanced pathology, also known as ultrastaging. At the authors’ institution, the protocol for SLN evaluation is described herein. The initial examination is performed using hematoxylin and eosin (H&E) staining. If the H&E assessment is negative, 2 adjacent 5-μg sections are cut from each paraffin block at each of 2 levels, 50 μg apart. At each level, one side is stained with H&E and the other with immunohistochemistry using the anticytokeratin AE1:AE3 (Ventana Medical Systems, Inc., Tucson, AZ) for a total of 4 slides per block. With immunohistochemistry ultrastaging, an additional 3% to 4% of micrometastases to SLNs, which may have been otherwise missed by routine H&E staining, can be detected. Tables 1 and 2 show the results of enhanced pathology and the added value of low-volume metastasis detection.

**SLN Mapping Algorithm**

Maintaining a low false-negative rate is a major priority in any SLN program. In a study of 498 patients

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**Table 1:** Incidence of H&E Macrometastases in Sentinel Lymph Nodes According to Final Histologic Grade and Depth of Myometrial Invasion

<table>
<thead>
<tr>
<th>DMI</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No invasion</td>
<td>H&amp;E 0</td>
<td>H&amp;E 1</td>
<td>H&amp;E 1</td>
<td>2/242=0.8%</td>
</tr>
<tr>
<td></td>
<td>n=165</td>
<td>n=39</td>
<td>n=38</td>
<td></td>
</tr>
<tr>
<td>&lt;50% invasion</td>
<td>H&amp;E 6</td>
<td>H&amp;E 4</td>
<td>H&amp;E 6</td>
<td>16/198=8.0%</td>
</tr>
<tr>
<td></td>
<td>n=80</td>
<td>n=62</td>
<td>n=56</td>
<td></td>
</tr>
<tr>
<td>≥50% invasion</td>
<td>H&amp;E 6</td>
<td>H&amp;E 3</td>
<td>H&amp;E 8</td>
<td>17/68=25.0%</td>
</tr>
<tr>
<td></td>
<td>n=16</td>
<td>n=15</td>
<td>n=37</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12/261=4.6%</td>
<td>8/116=6.9%</td>
<td>15/131=11.5%</td>
<td>35/508=6.9%</td>
</tr>
</tbody>
</table>

Abbreviations: DMI, depth of myometrial invasion; H&E, hematoxylin and eosin.

with endometrial cancer who received blue dye cervical injections at Memorial Sloan-Kettering Cancer Center from September 2005 to April 2011, the authors showed that incorporating an SLN mapping algorithm significantly reduced the false-negative rate of the procedure. An SLN was identified in 401 (81%) of the 498 patients, and correctly diagnosed metastatic nodal disease in 40 of 47 patients who had at least 1 SLN mapped (14.9% false-negative rate). Applying the algorithm decreased the false-negative rate to 1.9%, because the algorithm takes into account grossly enlarged suspicious nodes and includes a side-specific lymphadenectomy for the nonmapping hemipelvis. Only 1 patient with an isolated positive right para-aortic lymph node was not detected by the algorithm. Sensitivity increased from 85.1% to 98.1%, and the negative predictive value increased from 98.1% to 99.8% (Table 3).

The SLN surgical algorithm includes 1) peritoneal and serosal evaluation and washings; 2) retroperitoneal evaluation, including the removal of all SLNs and any suspicious nodes; and 3) a side-specific pelvic, common iliac, and interiliac lymph node dissection if there is no mapping on a hemipelvis. A para-aortic lymphadenectomy is left to the attending’s discretion (Figure 7).

Since incorporating the SLN mapping algorithm in 2008, the rate of full lymphadenectomy decreased from 65% to 23% at the author’s institution, with a parallel decrease in median operating room and operative times (≈1 hour and ≈40 minutes, respectively). The median number

### Table 2  Incidence of Ultrastage-Detected, Low-Volume Metastases in Sentinel Lymph Nodes According to Final Histologic Grade and Depth of Myometrial Invasion

<table>
<thead>
<tr>
<th>DMI</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No invasion</td>
<td>MM 1</td>
<td>MM 0</td>
<td>MM 0</td>
<td>2/242=0.8%</td>
</tr>
<tr>
<td>ITC 1 n=165</td>
<td>ITC 0</td>
<td>ITC 0</td>
<td>n=38</td>
<td></td>
</tr>
<tr>
<td>&lt;50% invasion</td>
<td>MM 2</td>
<td>MM 0</td>
<td>MM 0</td>
<td>16/198=8.0%</td>
</tr>
<tr>
<td>ITC 4 n=80</td>
<td>ITC 0</td>
<td>ITC 0</td>
<td>n=56</td>
<td></td>
</tr>
<tr>
<td>≥50% invasion</td>
<td>MM 0</td>
<td>MM 0</td>
<td>MM 1</td>
<td>5/68=7.4%</td>
</tr>
<tr>
<td>ITC 2 n=16</td>
<td>ITC 0</td>
<td>ITC 0</td>
<td>n=37</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10/261=3.8%</td>
<td>4/116=3.4%</td>
<td>9/131=6.9%</td>
<td>23/508=4.5%</td>
</tr>
</tbody>
</table>

Abbreviations: DMI, depth of myometrial invasion; ITC, isolated tumor cells; MM, micrometastasis.


### Table 3  Performance of SLN Mapping Alone Compared With the Algorithm for All Patients

<table>
<thead>
<tr>
<th>LN Positive</th>
<th>LN Negative</th>
<th>Total</th>
<th>SLN Alone</th>
<th>Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN positive</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Sensitivity</td>
<td>40/47</td>
</tr>
<tr>
<td>SLN negative</td>
<td>7</td>
<td>354</td>
<td>361</td>
<td>Negative predictive value</td>
<td>354/361</td>
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<tr>
<td></td>
<td>47</td>
<td>354</td>
<td>401</td>
<td>False-negative rate</td>
<td>7/47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LN Positive</th>
<th>LN Negative</th>
<th>Total</th>
<th>Algorithm</th>
<th>Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algorithm positive</td>
<td>53</td>
<td>0</td>
<td>53</td>
<td>Sensitivity</td>
<td>53/54</td>
</tr>
<tr>
<td>Algorithm negative</td>
<td>1</td>
<td>420</td>
<td>421</td>
<td>Negative predictive value</td>
<td>420/421</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>420</td>
<td>474</td>
<td>False-negative rate</td>
<td>1/54</td>
</tr>
</tbody>
</table>

Abbreviations: LN, lymph node; SLN, sentinel lymph node.

of nodes removed also decreased (from 20 to 7). Note, although this article previously reported that 10 or more lymph nodes were required for adequate surgical staging, this benchmark is associated with standard lymphadenectomy and not SLN mapping. The point of SLN mapping is to reduce the number of nodes that need to be removed for staging by targeting those likely to contain metastasis in the hopes of avoiding more extensive dissections and maintaining the ability to find microscopic nodal disease. This decreased rate of comprehensive lymphadenectomy and number of nodes removed has not compromised the rate of detection of metastatic nodal involvement, even in stage IIIC disease.

Moving Forward With SLN Mapping

The current apprehension with SLN mapping is the associated detection and false-negative rates, a circumstance in which an SLN is found to be negative even though the lymph nodes are found to have metastasis during lymphadenectomy. A failed mapping, on the other hand, is a situation in which an SLN is not identified, which is the opposite of the detection rate, and in the author’s algorithm, a failed mapping requires a side-specific lymphadenectomy to exclude disease. In the 2009 study of 42 patients with a diagnosis of grade 1 endometrial carcinoma, all positive cases were detected by the SLN, with no false-negatives. The sensitivity of the SLN procedure in the 36 patients (86%) who had an SLN identified was 100%.

An acceptable SLN detection rate varies among practices, but a detection rate of 80% to 90% or greater is preferred. Khoury-Collado et al reported on 115 patients with endometrial cancer treated at the author’s institution from September 2005 to March 2009 to determine the SLN detection rate for these patients and how many SLN mapping cases a surgeon needed to perform to reach the 90% benchmark. During the early phase of the study (September 2005–December 2007), an SLN was identified in 50 of 64 cases (78%), with 2 false-negatives; and during the late phase (January 2008–March 2009), an SLN was identified in 48 of 51 cases (94%), with no false-negatives. Detection rates increased from 77% to 94% ($P = .033$) during the 2 periods, with surgeon experience (≥30 cases) playing an integral role.

With increasing surgeon experience and a corresponding increase in detection rates of 90% or greater, combined with a decrease in false-negative rates, SLN mapping can play a more prominent role in lymph node assessment and staging in early-stage endometrial cancer. For now, the standard in many practices continues to include a comprehensive lymphadenectomy versus no nodal assessment, but as its therapeutic benefit comes into question (ASTEC and the study by Panici et al) and its associated side effects continue to be reported, this may change. However, prospective studies to validate the use of SLN mapping in this patient population are needed and ongoing.

References

Posttest Questions

1. The standard treatment for early-stage endometrial cancer in many practices includes complete or selective pelvic and para-aortic lymphadenectomy for staging because accurate staging is essential for determining appropriate treatment.
   a. True
   b. False

2. SLN mapping is based on the concept that lymph drains ______ the tumor in the lymphatic system; therefore, if the SLN, or first node, is negative for metastasis, then the ensuing nodes should also be negative.
   a. towards
   b. away from
   c. around

3. Which of the following is/are SLN mapping techniques (based on site of injection)?
   a. uterine subserosal
   b. cervical
   c. endometrial via hysteroscopy
   d. all of the above
   e. both b and c