Techniques of sentinel lymph node identification for early-stage cervical and uterine cancer

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Abstract

Techniques for sentinel lymph node injections have varied over the years in both cervical and uterine malignancy lymph node mapping. There remains considerable variation in techniques, particularly for uterine malignancies. This review summarizes some of the techniques that have been published and are currently utilized in sentinel lymph node mapping for cervical and uterine malignancies.

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Sentinel lymph node mapping for cervical cancer

Lymphoscintigraphy

This procedure requires a cervical injection of 0.1–0.5 mCi radiolabeled filtered Tc 99m microsulfur colloid in 0.1–0.5 ml volume after a speculum examination is performed. The injection is given directly into the cervix using a Potocky needle (Cooper Surgical, Inc., Trumbull, CT) or spinal needle in the four quadrants closest to the area of normal cervix/tumor interface; alternatively, injections at the 3 and 9 o’clock positions can be made. In patients who have undergone a prior cone biopsy, the injection is given into the bed of the cone. The injection is given into the stroma of the cervix. The radiolabeled injection and disposal of syringes and other materials should be done by the Nuclear Medicine Department.

A preoperative lymphoscintigram is obtained after the injection (Fig. 1). Two series of pictures are obtained: immediate “dynamic images” and subsequent “static images” to localize the nodes. The localizing scan usually accompanies the patient to the operating room. The procedure continues as planned, either through laparoscopy or laparotomy. The sentinel node identification and removal is performed first. If no blue nodes are noted, a second injection of 2 ml of blue dye can be injected directly into the cervix.

Injection of the radioisotope may be performed the day prior to surgery or the morning of surgery.

The injection of isosulfan blue (Lymphazurin®) (Fig. 2A) or methylene blue (Fig. 2B) is given in the operating room at the time of the examination while the patient is under anesthesia. Isosulfan blue is a sterile aqueous solution packaged in 5 ml vials. No preparation is needed, and it can be stored at room temperature. A spinal needle or Potocky needle is used to inject a total of 4 ml of blue dye directly into the cervical stroma. The injection of blue dye is given into cervix next to the lesion (Fig. 3). A tenaculum can be used to assist in the stromal injection. The 4 ml of blue dye can be divided into four separate injections, one into each quadrant of the cervix (1 ml each). Alternatively, the injections can be given at the 3 and 9 o’clock positions, which correspond more to the parametria and avoid blue dye staining of the bladder flap secondary to the 12 o’clock injection. After the injection, the patient is prepped and draped in the usual sterile fashion. The adverse effects of isosulfan blue include allergic reactions (<1% of patients), such as localized swelling and pruritus of the hands, feet, abdomen, and neck. Severe reactions, including edema of the face and glottis, respiratory distress,
and shock, have been occasionally reported with other similar compounds. In rare instances, isosulfan blue can cause a transient drop in oxygen saturation as measured by pulse oximetry. Isosulfan blue will turn the urine blue-green for up to 24 h following injection. Contraindications include known hypersensitivity to phenylethane compounds.

Fig. 1. Bilateral external iliac sentinel lymph nodes were identified in a patient undergoing a radical trachelectomy; the remaining visualized nodes are secondary.

Fig. 2. (A) Isosulfan blue, (B) Methylene blue.

Fig. 3. The blue dye is injected directly into the cervical stroma, preferably at the 3 and 9 o’clock positions — 1 cm³ each.

Fig. 4. (A) C-Trak laparoscopic sentinel lymph node probe, (B) A handheld open-procedure sentinel lymph node gamma probe.
Fig. 5. (A) A blue right sentinel hypogastric lymph node; blue channels can be seen leading to the lymph node. (B) A blue right common iliac lymph node in a patient with endometrial cancer a few minutes following cervical and fundal injections. (C) Blue left pelvic lymphatic channels and a blue left external iliac sentinel lymph node following cervical injection of blue dye in a patient undergoing a hysterectomy for uterine cancer. (D) Blue lymphatic channels with two blue left external iliac lymph nodes in a patient undergoing a fertility-sparing radical vaginal trachelectomy. (E) Blue lymphatic channels with two blue left external iliac lymph nodes post Methylene blue injection into the cervix in a patient undergoing abdominal surgery.
Intraoperative identification of the sentinel node

The pelvic and paraaortic sentinel node(s) that are identified will be labeled as “hot” and/or “blue.” The location of the node should be recorded. Laparoscopic or open surgery gamma probes, such as the C-Trak laparoscopic sentinel lymph node probe (Fig. 4A) or a handheld open-procedure sentinel lymph node gamma probe (Fig. 4B), are used to detect hot nodes. A post-excision bed count of each lymphatic basin should be recorded after removal of the sentinel node(s) in each basin. The retroperitoneum is fully exposed and the blue nodes are identified. All hot nodes will be removed and labeled according to anatomic location (Figs. 5A–E).

Detecting parametrial sentinel lymph nodes by lymphoscin-tigraphy or blue dye is challenging. The gamma probe will detect cervical injection site activity (which is usually very hot) and will make it impossible to distinguish parametrial uptake of Tc 99m from injection site uptake; in addition, blue dye commonly dissipates in the paracervical tissue and makes the isolation of blue parametrial lymph nodes very difficult (Fig. 6).

Sentinel lymph node mapping for uterine cancer

Both a cervical and a fundal injection can be utilized; in addition, an endometrial injection technique via hysteroscopy may be performed. The cervical injection is described above, and although it may not seem logical to only inject the cervix when dealing with uterine cancer, a deep injection into the uterine cervix can provide excellent dye penetration to the region of the uterine vessels in many cases (Fig. 7). A combination of a cervical and fundal injection can be utilized (Fig. 8). The fundal injection of Lymphazurin® also can be performed via laparoscopy, using a long needle (Fig. 9).

Synopsis of data on sentinel node mapping in patients with uterine corpus cancer

Seven studies have used the subserosal myometrium as the site of injection of the marker to identify the sentinel lymph node (Table 1) [1–7].

Burke et al. [1] published the first report on the identification of sentinel nodes in endometrial cancer. In their series of 15 patients, at the time of laparotomy, they occluded the tubes with hemoclips and injected isosulfan blue into the subserosal myometrium of the uterine fundus at three midline sites. Identification and removal of dye-containing nodes was performed followed by the standard staging procedure. Deposition of dye in at least one node was observed in 67% of cases. Two out of four metastatic nodes did not contain blue dye (false-negative rate of 50%). Holub et al. and Gien et al. reported similar detection rates of 61.5% and 55%, respectively, using a
similar technique [3,4]. On the other hand, Echt et al. failed to identify any sentinel lymph nodes in their series of 8 patients [2].

Li et al. [5] reported a detection rate of 75% using 1% Methylene blue injected into the fundal subserosal myometrium and at the uterine isthmus. In their series of 20 patients, after the initial 5 patients in whom no sentinel node was identified due to technical details, the authors identified a sentinel node in the remaining 15 patients. Therefore, the 75% detection rate reported may be an underestimation of the real detection rate with this technique. Altgassen et al. recently reported on a new approach for the identification of the sentinel node during laparotomy [7]. They used eight subserosal injection sites (four ventrally and four dorsally) in their series, with a 92% detection rate, which is the highest detection rate described for subserosal injection. This technique may be similar to the technique described by Li et al. [5] and seems to indicate that the detection rate increases with the number of injections at different sites of the uterine corpus.

Frumovitz et al. [6] reported on their series of 18 patients with clinical stage I endometrial cancer. This is the only study using both radioactive colloid and blue dye injection in the subserosal myometrium. The identification of sentinel lymph nodes was performed by a handheld gamma counter or by direct observation of blue discoloration of lymph nodes. The detection rate for a sentinel lymph node was only 45%. Surprisingly, this technique performed less well than when only blue dye was used by the same group [1]. The reason for this unexpected low rate of detection is not clear.

**Cervical injection**

Seven studies have used the cervix as the site of injection, either exclusively [8–12] or in combination with an injection into the subserosal myometrium [3,13] (Table 2) [3,8–13].

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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Substance injected</th>
<th>Site of injection</th>
<th>PAN</th>
<th>SLN detection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al. (1996)</td>
<td>15</td>
<td>B</td>
<td>Subserosal myometrium (3 sites)</td>
<td>Yes</td>
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<tr>
<td>Echt et al. (1999)</td>
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<td>Subserosal myometrium (3 sites)</td>
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<td>Holub et al. (2002)</td>
<td>13</td>
<td>B</td>
<td>Subserosal myometrium (3 sites)</td>
<td>No</td>
<td>61.5</td>
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<td>Gien et al. (2005)</td>
<td>9</td>
<td>B</td>
<td>Subserosal myometrium (1 site overlying the tumor)</td>
<td>Yes (for PS and CC)</td>
<td>56</td>
</tr>
<tr>
<td>Li et al. (2007)</td>
<td>20</td>
<td>B</td>
<td>Subserosal myometrium (3 sites) and Subserosal isthmus (2 sites)</td>
<td>Yes (4 cases)</td>
<td>75</td>
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<td>Frumovitz et al. (2007)</td>
<td>18</td>
<td>R,B</td>
<td>Subserosal myometrium (3 sites)</td>
<td>Yes</td>
<td>45</td>
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<td>Altgassen et al. (2007)</td>
<td>23</td>
<td>B</td>
<td>Subserosal myometrium (8 sites)</td>
<td>Yes (15 cases)</td>
<td>92</td>
</tr>
</tbody>
</table>

N, number of patients; PAN, periaortic nodes sampled; SLN, sentinel lymph node.  
B, blue dye; R, radiolabeled; PS, papillary serous; CC, clear cell.  
* Study using more than one site of injection and included in the other tables.
First, a radioactive tracer is injected into the cervix at 3, 6, 9 and 12 o’clock the day prior to surgery. A lymphoscintigraphy is then obtained after a certain number of hours (range, 1–18 h). Immediately prior to surgery, the blue dye is injected into the same cervical sites. Intraoperative identification of the sentinel lymph nodes is done by a handheld gamma probe and by direct visualization of blue colored nodes.

The rate of identification of a sentinel node varied from 80% to 100%. In the five studies using both blue dye and radioactive colloid, the detection rate was exactly the same for both the radioactive tracer and the blue dye in three studies [8–10] while a higher detection rate was achieved by the radioactive tracer in the other two studies [11,12]. In the latter two studies [11,12], however, 3 patients had metastatic nodes that were stained blue but had no radioactivity detected, leading to the consideration not to abandon the blue dye as an adjunct to the radioactive tracer if this technique is being used.

Holub et al. used a combination of cervical and subserosal injections of blue dye [3,13] and also reported a detection rate in the 80% range. A potential concern with cervical injection is that the nodal spread patterns are somewhat different for cervical and endometrial cancers, so it is debatable whether injections into the cervix could give reliable information on sentinel nodes in endometrial cancer. However, deep cervical injections at the 3 and 9 o’clock positions (with 2 ml of Lymphazurin® in each site) prior to a total hysterectomy may perform 10 min later and again the next day prior to surgery. Sentinel nodes were identified intraoperatively by a gamma probe and removed. Pelvic and paraaortic lymphadenectomies were then performed along with a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Detection rate was reported to be 82%, with 100% sensitivity and 100% specificity. The location of sentinel nodes identified in this report appears similar to the location of metastatic nodes identified in other studies examining spread patterns in endometrial cancer, with an incidence of metastatic lymph nodes of approximately 50% in the pelvis, 30% in both the pelvis and the paraaortic area, and 20% in the paraaortic area alone [18,19].

### Hysteroscopic injection

Five studies have used the technique of hysteroscopic injection to identify sentinel nodes (Table 3) [4,14–17]. This technique is more complicated and demanding than the direct cervical or uterine corpus injection as it requires hysteroscopic evaluation.

Niikura et al. [14], in their series of 28 patients, injected radioactive fluid around the tumor under direct visualization by hysteroscopy the day prior to surgery. The injections were performed at four sites under the endometrium around the tumor, and blue dye was used only to ensure the absence of leakage and not to identify sentinel nodes. For patients with multiple diffuse tumors in the uterine cavity, five injection sites covering the entire uterine cavity were used. Lymphoscintigraphy was performed 10 min later and again the next day prior to surgery. Sentinel nodes were identified intraoperatively by a gamma probe and removed. Pelvic and paraaortic lymphadenectomies were then performed along with a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Detection rate was reported to be 82%, with 100% sensitivity and 100% specificity. The location of sentinel nodes identified in this report appears similar to the location of metastatic nodes identified in other studies examining spread patterns in endometrial cancer, with an incidence of metastatic lymph nodes of approximately 50% in the pelvis, 30% in both the pelvis and the paraaortic area, and 20% in the paraaortic area alone [18,19].

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Substance injected</th>
<th>Site of injection</th>
<th>PAN</th>
<th>SLN detection (%)</th>
</tr>
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<tbody>
<tr>
<td>Cervical injection only</td>
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<td>Gargiulo et al. (2003) [8]</td>
<td>11</td>
<td>R,B</td>
<td>Cervix (3,6,9,12 o’clock)</td>
<td>No</td>
<td>100</td>
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<td>Pelosi et al. (2003) [9]</td>
<td>16</td>
<td>R,B</td>
<td>Cervix (3,6,9,12 o’clock)</td>
<td>No</td>
<td>94</td>
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<tr>
<td>Barranger et al. (2004) [10]</td>
<td>17</td>
<td>R,B</td>
<td>R: Cervix (3,6,9,12 o’clock) B: Cervix (3,9 o’clock)</td>
<td>No</td>
<td>94</td>
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<tr>
<td>Lelievre et al. (2004) [11]</td>
<td>12</td>
<td>R,B</td>
<td>Cervix (3,6,9,12 o’clock)</td>
<td>Yes (5 cases)</td>
<td>91</td>
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<tr>
<td>Bats et al. (2005) [12]</td>
<td>26</td>
<td>R,B</td>
<td>Cervix (3,6,9,12 o’clock)</td>
<td>No</td>
<td>80</td>
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Combined cervical and subserosal myometrium

<table>
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<tr>
<th>Study</th>
<th>N</th>
<th>Substance injected</th>
<th>Site of injection</th>
<th>PAN</th>
<th>SLN detection (%)</th>
</tr>
</thead>
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<tr>
<td>Holub et al. (2002) [3]</td>
<td>12</td>
<td>B</td>
<td>Cervix (3,6,9,12 o’clock) and Subserosal myometrium (1 site fundal)</td>
<td>No</td>
<td>83</td>
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<tr>
<td>Holub et al. (2004) [13]</td>
<td>25</td>
<td>B</td>
<td>Cervix (3,6,9,12 o’clock) and Subserosal myometrium (1 site fundal)</td>
<td>Yes (1 case)</td>
<td>84</td>
</tr>
</tbody>
</table>

N, number of patients; PAN, periaortic nodes sampled; SLN, sentinel lymph node.
B, blue dye; R, radiolabeled.

a Study using more than one site of injection and included in the other tables.

### Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Substance injected</th>
<th>Site of injection</th>
<th>PAN</th>
<th>SLN detection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysteroscopic</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raspagliesi et al. (2004) [16]</td>
<td>18</td>
<td>R,B</td>
<td>Endometrium</td>
<td>Yes (for PS and CC)</td>
<td>100</td>
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<tr>
<td>Maccauro et al. (2005) [17]</td>
<td>26</td>
<td>R, B</td>
<td>Endometrium</td>
<td>Yes (for PS and CC)</td>
<td>100</td>
</tr>
<tr>
<td>Gien et al. (2005) [4]</td>
<td>3</td>
<td>B</td>
<td>Endometrium</td>
<td>Yes (for PS and CC)</td>
<td>0</td>
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</table>

Hysteroscopic and subserosal myometrium

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Substance injected</th>
<th>Site of injection</th>
<th>PAN</th>
<th>SLN detection (%)</th>
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<tr>
<td>Gien et al. (2005) [4]</td>
<td>4</td>
<td>B</td>
<td>Endometrium and Subserosal myometrium (1 site overlying the tumor)</td>
<td>Yes (for PS and CC)</td>
<td>50</td>
</tr>
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</table>

N, number of patients; PAN, periaortic nodes sampled; SLN, sentinel lymph node.
B, blue dye; R, radiolabeled; PS, papillary serous; CC, clear cell.
a Study using more than one site of injection and included in the other tables.
Maccauro et al. and Raspagliesi et al. [16,17] evaluated both a radioactive tracer and blue dye injected hysteroscopically for the identification of sentinel nodes. Using a slight modification of the technique described by Niikura et al. [4], they obtained a lymphoscintigraphy 15 min after the hysteroscopic injection and then every 5 min for up to 1 h or until two or three sentinel nodes were identified. Surgery was performed within 3–4 h of the injection using an intraoperative gamma probe and direct identification of blue-stained nodes. After the removal of sentinel nodes, a pelvic lymphadenectomy was performed in all cases, and a paraaortic lymphadenectomy was performed only in cases of serous or clear cell histology. The authors reported that scintigraphy had a 100% success rate in detecting sentinel nodes, while the success rate for blue dye was only in the 30% range in both studies. In addition, they reported that all metastatic nodes were part of the sentinel nodes.

In their series of 10 patients, on the other hand, Fersis et al. reported only a 50% detection rate [15]. Gien et al. used hysteroscopic injection of blue dye alone [4]. In their first 3 patients, no sentinel node was detected. In their following 4 patients, they used both subserosal and hysteroscopic injections and were only able to achieve a 50% detection rate. The reason for this lower detection rate is not clear but may be due to the small number of patients included in these last two studies [4,15].

One of the theoretical concerns when performing hysteroscopic injection in patients with endometrial cancer is the risk of disseminating malignant cells through the tubes. Hysteroscopic visualization of the endometrial cavity can be achieved with pressures of 40 mmHg, which is lower than the 70 mmHg pressure needed for tubal spillage to occur [20]. Maccauro et al. and Raspagliesi et al. [16,17], in their respective series of 26 and 14 patients, each reported only 1 patient with positive peritoneal cytology. Gien et al. took peritoneal washings after the hysteroscopic procedure and found no cases of positive peritoneal cytology [4].

### False-negative rates

Achieving an acceptably low false-negative rate is crucial before lymph mapping can be considered as an alternative to the current treatment standards. Although the false-negative rate obtained in many series is 0% [2,8–11,13–17], the number of patients studied in the different case series published varied between 8 and 28 patients. Due to this limited number of patients, in addition to the relatively low incidence of lymph node metastasis in early-stage endometrial cancer, a large number of patients is needed in order to calculate clinically significant sensitivity and false-negative rates since the statistical analysis is based on the number of node-positive patients [6]. As with any other new surgical technique, it is essential that physicians determine their false-negative rates in their respective practice environments to ensure patient safety and avoid undertreatment.

### Conflict of interest statement

The authors have no conflicts of interest to declare.

### References


