Published in final edited form as:

Gynecol Oncol. 2012 December ; 127(3): 467–471. doi:10.1016/j.ygyno.2012.08.015.

“Triple injection” lymphatic mapping technique to determine if parametrial nodes are the true sentinel lymph nodes in women with cervical cancer

Michael Frumovitz, MD, MPH^{a,*}, Elizabeth D. Euscher, MD^b, Michael T. Deavers, MD^b, Pamela T. Soliman, MD, MPH^a, Kathleen M. Schmeler, MD^a, Pedro T. Ramirez, MD^a, and Charles F. Levenback, MD^a

^aDepartment of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

^bDepartment of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

Objectives—Lymphatic mapping studies in women with cervical cancer typically identify sentinel nodes (SLNs) in the pelvis and not the parametrium. We added India ink as a mapping agent to determine whether this would allow us to pathologically identify sentinel parametrial nodes and to test our hypothesis that the parametrial nodes are the true SLNs in women with cervical cancer.

Methods—We performed lymphatic mapping and SLN biopsy in 20 women with early-stage cervical cancer undergoing radical hysterectomy or trachelectomy using a “triple injection” technique with blue dye, radiocolloid, and India ink. Pathologic processing of parametrium and nodal tissue was then performed to identify India ink in specimens.

Results—On pathology review, 15 (75%) patients had a parametrial node identified, and 9 patients (45%) had bilateral parametrial nodes identified; the median number of parametrial nodes identified was 2 (range, 0–7). India ink was seen in at least 1 parametrial node in 13 (87%) of the 15 patients with a parametrial node identified pathologically. Of the 9 patients with bilateral parametrial nodes identified pathologically, only 5 (54%) had bilateral parametrial nodes containing India ink. India ink was found in 26 (44%) of 59 SLNs and only 1 (0.3%) of 289 non-SLNs. In 5 patients, India ink was seen in a SLN on the same side of the pelvis where a parametrial node was identified but not microscopically black.

Conclusions—There appears to be direct drainage of cervical lesions to pelvic nodal basins bypassing small parametrial nodes. Parametrial nodes, therefore, may not always be the SLNs in women with cervical cancer.

© 2012 Elsevier Inc. All rights reserved.

*Corresponding author: Michael Frumovitz, MD, MPH, Department of Gynecologic Oncology, CPB6.3244, Unit 1362, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler, Houston, TX 77030. Phone: (713) 592-9599. Fax: (713) 792-7586. mfrumovitz@mdanderson.org..

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: The authors have no conflicts of interest to disclose

Keywords

cervix; sentinel node; lymphatic mapping; parametrium

Introduction

Radical hysterectomy and complete pelvic lymphadenectomy has long been the standard treatment for early-stage cervical cancer. Pelvic lymphadenectomy, however, may lead to lymphedema, lymphocysts, and urologic complications [1]. In addition, up to 20% of patients with clinically early stage disease have pelvic or paraaortic lymph node metastasis detected at lymphadenectomy and require adjuvant radiotherapy, which significantly increases the risk of complications compared to surgery or radiotherapy alone [2]. For these reasons, lymphatic mapping and sentinel lymph node biopsy in patients with early-stage cervical cancer has been explored [3-8]. The potential advantage of this technique in these patients is to reduce the extent of lymph node dissection and thereby minimize the probability of complications associated with complete lymphadenectomy and postoperative radiotherapy should it be required. In addition, identification of sentinel nodes allows the pathologist to perform immunohistochemical staining, use of which is not practical or cost-effective when a large number of nodes need to be examined but is feasible when only sentinel nodes need to be examined; this “ultrastaging” increases the identification of metastatic disease compared with the standard methods of examining lymph nodes [9].

The published studies on lymphatic mapping and sentinel node biopsy for patients with cervical cancer show high rates of detection of sentinel nodes. In one of the earliest publications on the subject, Levenback et al. [3] performed lymphatic mapping and sentinel node biopsy in 39 patients with cervical cancer undergoing laparotomy with radical hysterectomy and retroperitoneal lymph node dissection and found that in the detection of metastasis in retroperitoneal lymph nodes, the sentinel node technique had a sensitivity of 87.5% and a negative predictive value of 97%. More recently, the SENTICOL study, a prospective, multi-institutional French collaborative protocol, evaluated the sentinel node concept in 139 patients with early-stage cervical cancer. Overall, the authors reported that sentinel node biopsy had a sensitivity of 92.0% and a negative predictive value of 98.2%. Furthermore, in the 76.5% of patients in whom at least 1 sentinel node was found on each side of the body, there were no false-negative results [10].

Radical hysterectomy is predicated on the assumption that there are lymphatic channels and lymph nodes in the parametrium that should be resected in continuity with the primary tumor. The parametrial dissection, however, adds substantial morbidity to the surgery. In the multiple mapping studies that have been published, virtually all sentinel nodes have been described along the external iliac, internal iliac, and common iliac vessels, the vena cava, and the aorta and in the presacral region [11]. Is this because parametrial lymph nodes are not sentinel or because the mapping techniques employed fail to identify parametrial sentinel nodes?

The parametrial nodes may be the first nodes to drain primary cervical tumors as they are anatomically the closest nodes to such tumors. However, very few studies have reported the identification of a significant number of sentinel nodes in the parametrial tissue, and none of the previous studies have tried to determine whether the parametrial nodes are the true sentinel nodes and the pelvic and paraaortic nodes are second-echelon nodes.

With the agents currently used for mapping—blue dye and radiocolloid—it is virtually impossible to identify potential sentinel nodes in the parametrium on microscopic sections.

Unfortunately, visualization of blue dye within the parametrial nodes is difficult as these nodes can be quite small and are often obscured within the thick parametrial tissue. Furthermore, by the time the pathologist identifies these nodes on histologic analysis, the blue dye most commonly used for lymphatic mapping, Lymphazurin, has been washed out in the pathologic processing. The use of radiocolloid to identify the parametrial nodes in situ is equally ineffective as the proximity of these nodes to the primary injection site makes them impossible to distinguish using a handheld gamma counter. Also, as peak counts quickly decay, by the time specimens get to the pathologist, they have lost much of their radioactivity. More importantly, most pathology laboratories are not properly equipped to detect the radiocolloid within potential sentinel nodes.

In 2001, Haigh and colleagues [12] published their experience with a “triple injection” technique for patients with malignant melanoma. Along with the commonly used blue dye and radiocolloid, they injected sterilized India ink as a third mapping agent. The carbon particles in the India ink “stained” sentinel nodes black, and the sentinel nodes remained black after pathologic processing (Figure 1), which allowed for microscopic pathologic identification of the sentinel nodes due to their black color in addition to preoperative identification of the sentinel nodes via imaging (lymphoscintigraphy or single photon emission computed tomography/computed tomography) and intraoperative identification via direct visualization of blue-stained nodes and/or detection of radioactivity (technetium-99). In addition, the authors found this technique to be “safe and nontoxic” in the 100 patients enrolled on protocol [12].

One purpose of the study reported herein was to determine whether adoption of this “triple injection” technique would allow us to pathologically identify sentinel parametrial nodes in women with cervical cancer. The other purpose of the study was to test our hypothesis that the parametrial nodes are the true sentinel nodes in patients with cervical cancer—more specifically, that pelvic or paraaortic nodes would not be stained with India ink if parametrial nodes were not stained with India ink.

Methods

After obtaining approval from The University of Texas MD Anderson Institutional Review Board and the US Food and Drug Administration (FDA), we prospectively enrolled 20 patients with cervical cancer undergoing radical hysterectomy or radical trachelectomy and pelvic lymphadenectomy. FDA approval was necessary because of the dearth of data on the safety of injecting the 3 compounds (radiolabeled technetium-99, Lymphazurin, and India ink) together. To be eligible for the study, patients could not have evidence of metastases on computed tomography, magnetic resonance imaging, or positron emission tomography/computed tomography scan, although preoperative imaging was not required. Patients who were pregnant, who had known allergies to triphenylmethane compounds or India ink, or who had had retroperitoneal surgery or pelvic irradiation were ineligible.

Lymphatic mapping and sentinel node identification

Lymphatic mapping and sentinel node biopsy were performed using a “triple injection” technique. After general anesthesia was induced but prior to prepping and draping of the patient, 2 ml of radiolabeled technetium-99 (0.5 mCi-1.0 mCi) was injected intradermally into 4 quadrants of the cervix. At that point, to allow adequate time for the radiocolloid to reach sentinel nodes, the patient was prepped and draped, and either the abdomen was opened (for laparotomy) or trocars were placed (for minimally invasive approaches).

After the abdomen was explored but before any of the pelvic procedures were started, 4 ml of Lymphazurin (U.S. Surgical Corporation, Norwalk, CT) was injected in 1-ml aliquots

intradermally into the cervix in 4 quadrants. Then, 4 ml of sterilized India ink (Endomark Endoscopic Inkmarker, PMT Corporation, Chanhassen, MN) was injected intradermally into the cervix in 4 quadrants. The retroperitoneal spaces were then opened, and with use of both direct visualization and a handheld gamma counter, the sentinel nodes were identified and removed. Sentinel nodes were labeled by location and labeled as “blue” (identified by direct visualization only), “hot” (identified by gamma counter only), or both.

Definitive surgery

Once the sentinel nodes had been identified and removed, all patients underwent a type II or III radical hysterectomy or radical trachelectomy by laparotomy, laparoscopy, or robotic surgery (DaVinci robotic system, Sunnyvale, CA), as well as a complete pelvic lymphadenectomy including removal of the common iliac lymph nodes. At the surgeon's discretion, the surgeon could perform a low paraaortic lymphadenectomy to encompass right and left paraaortic lymph nodes between the origin of the inferior mesenteric artery and the bifurcation of the aorta.

Histologic evaluation

As parametrial nodes are often difficult to see and as the high radioactivity of the primary cervical lesion makes it difficult to identify parametrial nodes using a gamma counter in parametrium attached to the radical hysterectomy specimen, the parametrium was separated from the cervix/uterus and then away from the primary cervical lesion and then re-examined for sentinel nodes both visually and with a handheld gamma counter. In addition, all parametrial tissue was submitted for pathologic sectioning to detect carbon particles in parametrial sentinel nodes not detected by gamma counter or direct visualization.

All parametrial and sentinel lymph nodes were serially sectioned perpendicular to the long axis at 2.0-mm intervals. Lymph nodes 0.5 cm and smaller were bisected. Blocks were then submitted for routine processing with hematoxylin and eosin (H&E). If a parametrial or sentinel node had a metastasis in the initial H&E-stained section, no further work-up was performed on that lymph node. If a sentinel node was negative on the initial section, ultrastaging was performed. This entailed performing 5 wide H&E levels at 250- μ m intervals. With each level, 2 unstained slides were cut (total of 10 unstained slides). If the wide H&E intervals were negative, 1 unstained slide at each level was subjected to immunostaining with pan-cytokeratin (Cytokeratin AE1/AE3, Dako Corp., Carpinteria CA; 1:50, Cytokeratin CAM5.2, BD Biosciences, San Jose, CA; 1:50, Cytokeratin MNF116, Dako Corp., Carpinteria, CA; 1:50 and Cytokeratin 8&18, Invitrogen, South San Francisco, CA ; 1:25) using polymeric biotin-free horseradish peroxidase (HRP) method on (Leica Microsystems, Bannockburn, IL) Bond Max stainer.

Sentinel nodes were classified according to a modification of the American Joint Committee on Cancer staging system for axillary nodes from breast cancer. The categories were (1) metastases present (tumor greater than 2.0 mm in diameter); (2) micrometastases present (tumor cell aggregates 0.2 to 2.0 mm in diameter); (3) isolated tumor cells (individual tumor cells or aggregates less than 0.2 mm in diameter, usually detected by immunohistochemistry); and (4) tumor absent (no tumor cells identified in H&E-stained [or immunohistochemically stained, if applicable] sections).

Results

From March 2009 to June 2011, 20 patients were enrolled on the protocol by 8 different surgeons. The median patient age was 35 years (range, 21-68), and the median body mass index was 25.2 kg/m² (range, 18.2-47.3). Patient demographics and tumor characteristics are

summarized in Table 1. Eleven (55%) patients underwent radical hysterectomy (open 3, laparoscopic 2, robotically assisted 6), and 9 (45%) underwent radical trachelectomy (open 5, robotically assisted 4).

Intraoperatively, at least 1 sentinel node was found in 17 (85%) of the 20 patients. A total of 59 sentinel nodes were found in these 17 patients. The median number of sentinel nodes found was 3 (range, 0-8). Of the 59 sentinel nodes found, 5 (8%) were blue only, 10 (17%) were hot only, and 44 (75%) were both blue and hot. (Table 2) Of the 17 patients in whom a sentinel node was found, 12 (71%) had bilateral sentinel nodes found (60% of the entire cohort had bilateral sentinel nodes identified). The locations of the identified sentinel nodes are summarized in Table 3. Ninety-two percent of the sentinel nodes were found in the pelvis; 5% were found along the common iliac vessels and 3% were found in a presacral location. Two hundred eighty-nine nonsentinel nodes were removed, and the median number of non-sentinel pelvic nodes per patient was 14.5 (range, 5-21).

Pathologically, a parametrial node was identified microscopically in 15 (75%) patients. Nine patients (45%) had bilateral parametrial nodes identified, while the remaining 6 patients (30%) had only unilateral parametrial nodes identified. The median number of parametrial nodes identified microscopically was 2 (range, 0-7).

Of the 15 patients who had a parametrial node found on pathologic sectioning, 13 (87%) had India ink seen in at least 1 parametrial node (median, 1; range, 0-4). Of the 9 patients with bilateral nodes found pathologically, only 5 (54%) had bilateral parametrial nodes containing India ink. India ink was found in 31 (53%) of 59 sentinel nodes and in only 1 (0.3%) of 289 nonsentinel nodes. (Table 2) On pathologic processing, India ink was seen in a pelvic sentinel node on the same side of the pelvis where a parametrial node was identified pathologically but not black in 5 patients suggesting lymphatic drainage directly to the pelvic sidewall bypassing the parametrial nodes.

Five patients (25%) had metastasis to lymph nodes. Three patients had a pathologically positive sentinel node in the pelvis identified intraoperatively. In these 3 patients, there were no positive nonsentinel nodes. One patient had a macrometastasis found on H&E staining, 1 patient had a micrometastasis found on H&E staining, and 1 patient had a micrometastasis found on immunohistochemical staining. Of the 3 patients with pathologically positive sentinel nodes, 2 had no parametrial nodes identified, but the third had 2 parametrial nodes identified on the side where the positive sentinel node was identified. However, neither of these nodes had India ink seen in them. One patient had metastatic disease found in a parametrial node on H&E staining. Although this node was not identified intraoperatively as a sentinel node, it did contain India ink when evaluated pathologically (Figure 1). The final patient had a pelvic node containing tumor but had no sentinel nodes identified intraoperatively and no parametrial nodes identified pathologically.

Discussion

Using a “triple injection” technique with blue dye, radiocolloid, and India ink, we were able to pathologically identify a parametrial node as “sentinel” in 87% of patients who had parametrial nodes present. However, only 54% of the patients with bilateral nodes seen in the parametrium had black ink seen bilaterally. Furthermore, 5 patients (25%) had India ink seen in a pelvic sentinel node on the same side where parametrial nodes had no India ink, suggesting direct drainage from the cervix to the pelvic sidewall bypassing nodes in the parametrium.

Previous pathologic studies have attempted to discern whether positive pelvic or paraaortic lymph nodes exist in the absence of positive parametrial nodes. However, to the best of our

knowledge, this is the first study to do so with lymphatic mapping techniques. Using “giant section” pathologic processing of the parametrium, Benedetti-Panici et al. [13] found that all patients with pelvic lymph node metastasis also had parametrial involvement. Yen et al. [14] confirmed this finding: they found that 96% of their patients with pelvic nodal involvement also had parametrial nodal involvement. In contrast, Girardi et al. [15] found that only 74% of patients with positive pelvic nodes had positive parametrial nodes. All of these studies, however, included a significant number of patients with greater than stage IB1 disease, and much of the corresponding parametrial involvement was due to direct extension of tumor into the parametrium and not due to tumor emboli in parametrial nodes. For example, in the study by Benedetti-Panici et al., 60% of patients with stage IB2-IIA disease had parametrial involvement, yet half of these cases were due to direct tumor extension into the parametrium.

Similar to the studies described above, our protocol systematically submitted the entire parametrium; however, our study was limited to patients with small-volume disease without direct extension from the primary lesion into the parametrium. In our cohort of 20 patients, 5 had metastatic disease to lymph nodes: 1 with metastasis in a parametrial node and 4 patients with disease spread to nodes along the iliac vessels (pelvic nodes). Of these latter 4 patients, one had disease that seemingly skipped the ipsilateral parametrial node, while the other 3 had no ipsilateral parametrial nodes identified on the side where the pelvic node contained disease. These findings are similar to those reported by Covens et al., who reported minimal correlation between pelvic and parametrial nodes: only 26% of the patients in their study with positive pelvic nodes also had positive parametrial nodes. In other words, 74% of the patients in their study had direct metastasis to the pelvic lymph nodes with no parametrial involvement [16]. Our mapping study also supports a route of direct lymphatic drainage from the cervical tumor to the pelvic nodes that seemingly bypasses the parametrial nodes.

On examination of the entire parametrium, 75% of our patients had at least 1 parametrial node identified. This rate is similar to the rate reported by Girardi et al. [15], who identified a parametrial node in 78% of radical hysterectomy specimens, but less than the rate reported by Benedetti-Panici et al. [13], who identified a parametrial node in 93% of specimens. Neither group reported whether parametrial nodes were unilateral or bilateral. In our cohort, however, only 45% of patients had bilateral parametrial nodes identified.

Overall, we found at least 1 sentinel node in 85% of patients enrolled and bilateral nodes in 60%. Of the 4 patients with metastatic disease in pelvic nodes, 3 had disease in sentinel nodes, while the fourth had disease in a pelvic node in the absence of sentinel node identification on that side of the pelvis. Some controversy exists as to whether detection of metastatic disease in a pelvic node on a side where mapping was unsuccessful should be considered a failure of the mapping technique. In a review of 122 cases of lymphatic mapping in women with cervical cancer, Cormier et al. [17] reported 25 patients with lymph node metastases, 21 of whom had metastases detected in sentinel nodes. The remaining 4 patients had metastases detected in pelvic nodes on sides where no sentinel nodes were detected. The authors proposed that in the absence of finding a sentinel node in one or both pelvic sidewalls, complete pelvic lymphadenectomy should be performed. Using this algorithm—only sentinel node biopsy when a sentinel node is found and complete pelvic lymphadenectomy when no sentinel node is found—they would have detected all cases of lymph node metastases [17]. A similar approach in our small series would have similarly yielded a 100% detection rate of metastatic disease in lymph nodes.

The “triple injection” technique described here is based on the traditional “double injection” technique of blue dye and radiocolloid. Although some surgeons currently only use either

blue dye or radiocolloid, we continue to advocate for their combined use. In this series, use of only blue dye would have missed the 17% of sentinel nodes detected that were hot only. Conversely, using only radiocolloid would have missed the 8% of sentinel nodes that were blue only. Multiple authors have reported increasing their sentinel node detection rate from 70-80% to over 90% with the addition of blue dye to radiocolloid alone [18] or radiocolloid to blue dye alone [19, 20]. We also remain convinced that the combined technique improves sentinel node detection in women with gynecologic malignancies.

The addition of India ink as a third mapping substance, however, did not significantly increase detection of sentinel nodes in the pelvis. In fact, India ink alone identified only a single pelvic sentinel node (0.3%) not detected with blue dye and/or radiocolloid. However, the addition of India ink did confirm that sentinel nodes detected by traditional mapping substances are likely true sentinel nodes and not second-echelon nodes detected by blue dye that had already passed through sentinel nodes.

In addition to shedding light on the question of which nodes are the “true” sentinel nodes in cervical cancer, this study may provide insight into the debate about the importance of performing a parametrectomy for early-stage cervical cancer (stages IA2-IB1). When we remove the parametrium in women with cervical cancer, are we resecting disease or just the lymphatic channels draining the primary tumor? For women with vulvar cancer, gynecologic oncologists abandoned en bloc resection of the vulva, groin nodes, and intervening skin bridge with its rich lymphatic channels in favor of the less morbid double- or triple-incision approach. Our findings in this study show a direct route of drainage from the cervix to the pelvic nodes bypassing parametrial nodes. In addition, 25% of patients had no parametrial nodes identified at all. This seems to correlate closely with our previous finding that 15% of patients with parametrial spread had tumor found only in lymphatic channels and not in nodal or stromal tissue [21]. Many authors, including our group, have long argued for the existence of a cohort of patients with cervical cancer who are at low risk for parametrial spread and in whom parametrectomy may be excluded [16, 21-25].

In conclusion, we were unable to identify parametrial nodes in many of the parametrial specimens examined. In addition, even in the presence of parametrial lymph nodes, there appears to be direct drainage of cervical lesions to the pelvic nodal basins bypassing these small parametrial nodes. Finally, although the addition of India ink yielded interesting insight into how lymphatic spread from the cervix may occur, for practical purposes outside of a study such as this, we do not recommend adding India ink as a third mapping substance.

Acknowledgments

This research was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant, CA016672.

References

1. Benedetti-Panici P, Maneschi F, Cutillo G, D'Andrea G, di Palumbo VS, Conte M, Scambia G, Mancuso S. A randomized study comparing retroperitoneal drainage with no drainage after lymphadenectomy in gynecologic malignancies. *Gynecol Oncol.* 1997; 65:478–82. [PubMed: 9190979]
2. Burke TW. Treatment Options in Stage IB Cervical Cancer: Radical Hysterectomy and Radiotherapy. *Semin Radiat Oncol.* 1994; 4:34–40. [PubMed: 10717088]
3. Levenback C, Coleman RL, Burke TW, Lin WM, Erdman W, Deavers M, Delpassand ES. Lymphatic mapping and sentinel node identification in patients with cervix cancer undergoing radical hysterectomy and pelvic lymphadenectomy. *J Clin Oncol.* 2002; 20:688–93. [PubMed: 11821449]

4. Pijpers R, Buist MR, van Lingen A, Dijkstra J, van Diest PJ, Teule GJ, Kenemans P, Verheijen RH. The sentinel node in cervical cancer: scintigraphy and laparoscopic gamma probe-guided biopsy. *Eur J Nucl Med Mol Imaging*. 2004; 31:1479–86. [PubMed: 15221288]
5. Niikura H, Okamura C, Akahira J, Takano T, Ito K, Okamura K, Yaegashi N. Sentinel lymph node detection in early cervical cancer with combination 99mTc phytate and patent blue. *Gynecol Oncol*. 2004; 94:528–32. [PubMed: 15297199]
6. Gil-Moreno A, Diaz-Feijoo B, Roca I, Puig O, Perez-Benavente MA, Aguilar I, Martinez-Palones JM, Xercavins J. Total laparoscopic radical hysterectomy with intraoperative sentinel node identification in patients with early invasive cervical cancer. *Gynecol Oncol*. 2005; 96:187–93. [PubMed: 15589599]
7. van Dam PA, Hauspy J, Vanderheyden T, Sonnemans H, Spaepen A, Eggenstein G, Dirix L, Verkinderen L. Intraoperative sentinel node identification with Technetium-99m-labeled nanocolloid in patients with cancer of the uterine cervix: a feasibility study. *Int J Gynecol Cancer*. 2003; 13:182–6. [PubMed: 12657121]
8. O'Boyle JD, Coleman RL, Bernstein SG, Lifshitz S, Muller CY, Miller DS. Intraoperative lymphatic mapping in cervix cancer patients undergoing radical hysterectomy: A pilot study. *Gynecol Oncol*. 2000; 79:238–43. [PubMed: 11063651]
9. Euscher ED, Malpica A, Atkinson EN, Levenback CF, Frumovitz M, Deavers MT. Ultrastaging improves detection of metastases in sentinel lymph nodes of uterine cervix squamous cell carcinoma. *Am J Surg Pathol*. 2008; 32:1336–43. [PubMed: 18670356]
10. Lecuru F, Mathevet P, Querleu D, Leblanc E, Morice P, Darai E, Marret H, Magaud L, Gillaizeau F, Chatellier G, Dargent D. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol*. 2011; 29:1686–91. [PubMed: 21444878]
11. Marnitz S, Kohler C, Bongardt S, Braig U, Hertel H, Schneider A. Topographic distribution of sentinel lymph nodes in patients with cervical cancer. *Gynecol Oncol*. 2006; 103:35–44. [PubMed: 16600355]
12. Haigh PI, Lucci A, Turner RR, Bostick PJ, Krasne DL, Stern SL, Morton DL. Carbon dye histologically confirms the identity of sentinel lymph nodes in cutaneous melanoma. *Cancer*. 2001; 92:535–41. [PubMed: 11505397]
13. Benedetti-Panici P, Maneschi F, D'Andrea G, Cutillo G, Rabitti C, Congiu M, Coronetta F, Capelli A. Early cervical carcinoma: the natural history of lymph node involvement redefined on the basis of thorough parametrectomy and giant section study. *Cancer*. 2000; 88:2267–74. [PubMed: 10820348]
14. Yen MS, Yuan CC, Wang PH, Ng HT, Twu NF, Juang CM. Parametrial tumor spreading patterns in cervix cancer patients treated by radical hysterectomy. *Int J Gynaecol Obstet*. 2003; 80:145–51. [PubMed: 12566187]
15. Girardi F, Lichtenegger W, Tamussino K, Haas J. The importance of parametrial lymph nodes in the treatment of cervical cancer. *Gynecol Oncol*. 1989; 34:206–11. [PubMed: 2753426]
16. Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, Colgan T, Chapman W, Shaw P. How important is removal of the parametrium at surgery for carcinoma of the cervix? *Gynecol Oncol*. 2002; 84:145–9. [PubMed: 11748991]
17. Cormier B, Diaz JP, Shih K, Sampson RM, Sonoda Y, Park KJ, Alektiar K, Chi DS, Barakat RR, Abu-Rustum NR. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. *Gynecol Oncol*. 2011; 122:275–80. [PubMed: 21570713]
18. Malur S, Krause N, Kohler C, Schneider A. Sentinel lymph node detection in patients with cervical cancer. *Gynecol Oncol*. 2001; 80:254–7. [PubMed: 11161868]
19. Plante M, Renaud MC, Tetu B, Harel F, Roy M. Laparoscopic sentinel node mapping in early-stage cervical cancer. *Gynecol Oncol*. 2003; 91:494–503. [PubMed: 14675667]
20. Rob L, Strnad P, Robova H, Charvat M, Pluta M, Schlegelova D, Hrehorcak M. Study of lymphatic mapping and sentinel node identification in early stage cervical cancer. *Gynecol Oncol*. 2005; 98:281–8. [PubMed: 15961145]

21. Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF, Ramirez PT. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. *Obstet Gynecol.* 2009; 114:93–9. [PubMed: 19546764]
22. Kinney WK, Hodge DO, Egorshin EV, Ballard DJ, Podratz KC. Identification of a low-risk subset of patients with stage IB invasive squamous cancer of the cervix possibly suited to less radical surgical treatment. *Gynecol Oncol.* 1995; 57:3–6. [PubMed: 7705699]
23. Steed H, Capstick V, Schepansky A, Honore L, Hiltz M, Faught W. Early cervical cancer and parametrial involvement: is it significant? *Gynecol Oncol.* 2006; 103:53–7. [PubMed: 16516279]
24. Stegeman M, Louwen M, van der Velden J, ten Kate FJ, den Bakker MA, Burger CW, Ansink AC. The incidence of parametrial tumor involvement in select patients with early cervix cancer is too low to justify parametrectomy. *Gynecol Oncol.* 2007; 105:475–80. [PubMed: 17292460]
25. Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, Rader JS, Mutch DG. Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. *Cancer.* 2007; 110:1281–6. [PubMed: 17654664]

Research Highlights

- When present, parametrial nodes are “sentinel” 87% of the time.
- Only 54% of the patients with bilateral nodes in the parametrium had black ink seen bilaterally.
- There appears to be direct drainage from the cervix to the pelvic sidewall bypassing nodes in the parametrium.

Figure 1.

Photomicrographs of parametrial lymph nodes from study cases: 1A) 1.0 mm lymph node representative of the small lymph nodes typically identified in sections of parametrium (10x); 1B higher power image of the same lymph node with focal India ink in the superficial cortex (arrow, 40x); 1C, parametrial lymph node with a < 1.0 mm focus of metastatic squamous cell carcinoma (arrows, 10x); 1D, very small focus of India ink present in the superficial cortex adjacent to the metastasis (arrow, 40x).

Table 1

Patient and tumor characteristics (n = 20)

Characteristic	Number of patients	Percentage
Median age (range)	35 years (21-68)	
Median body mass index (range)	25.2 kg/m ² (18.2-47.3)	
Histologic subtype		
Squamous	14	70
Adenocarcinoma	2	10
Adenosquamous	3	15
Neuroendocrine	1	5
Stage		
IA1	2	10
IA2	3	15
IB1	14	70
IIA	1	5
Prior cone biopsy		
Yes	9	45
No	11	55
Visible lesion?		
Yes	10	50
No	10	50
Median tumor size (range) *	2 cm (1-4)	
Lymphovascular space invasion?		
Yes	16	80
No	4	20

* Median tumor size calculated from visible lesions only.

Table 2

Mapping substances detected in sentinel lymph nodes intraoperatively and microscopically (n = 59)

Mapping Substances	Intraoperative Identification	Microscopic Identification (India ink)
Blue dye only	5 (8%)	1 (20%)
Radiocolloid only	10 (17%)	5 (50%)
Blue dye and radiocolloid	44 (25%)	25 (57%)

Table 3

Locations of intraoperatively detected sentinel lymph nodes (n = 59)

Location	Number of nodes	Percentage
Parametrial		
Right	3	5
Left	2	3
Obturator/internal iliac		
Right	18	31
Left	13	22
External iliac		
Right	11	19
Left	7	12
Common iliac		
Right	3	5
Left	0	0
Presacral	2	3