Published in final edited form as:

Gynecol Oncol. 2017 April ; 145(1): 96–101. doi:10.1016/j.ygyno.2017.02.005.

Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer

Gloria Salvo^a, Pedro T. Ramirez^a, Charles F. Levenback^a, Mark F. Munsell^b, Elizabeth D. Euscher^c, Pamela T. Soliman^a, and Michael Frumovitz^{a,*}

^aDepartment of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, United States

^bDepartment of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, United States

^cDepartment of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, United States

Abstract

Objective—The role of sentinel lymph node (SLN) biopsy alone for staging of early-stage cervical cancer remains controversial. We aimed to determine the validity of this technique in women with early-stage cervical cancer.

Methods—We retrospectively reviewed women with early-stage cervical cancer who underwent SLN mapping followed by complete pelvic lymphadenectomy as part of initial surgical management from August 1997 through October 2015. All modes of surgical approach were included. Lymphatic mapping was performed using blue dye, technetium-99m sulfur colloid (Tc-99), and/or indocyanine green (ICG). We determined SLN detection rates, sensitivity and negative predictive value.

Results—One hundred eighty-eight patients were included, and 35 (19%) had lymph node metastases. At least one SLN was identified in 170 patients (90%), and bilateral SLNs were identified in 117 patients (62%). The majority of SLNs (83%) were found in the pelvis. There was no difference in detection rates between mapping agents, surgical approach, patients with and without prior conization or between patients with tumors < 2 cm and ≥ 2 cm. The detection rate for bilateral SLNs was significantly lower in women with body mass index (BMI) > 30 kg/m² than in women with lower BMI ($p=0.03$). Metastatic disease in sentinel nodes was detected by H&E staining in 78% of cases and required ultrastaging/immunohistochemistry in 22% of cases. Only

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

Conflict of Interest: Dr. Michael Frumovitz receives research funding from Navidea and Novadaq and serves as a consultant to Novadaq

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.

one patient had a false-negative result, yielding a sensitivity of 96.4% (95% CI 79.8%–99.8%) and negative predictive value of 99.3% (95% CI 95.6%–100%). The false-negative rate was 3.6%.

Conclusions—In these women with early-stage cervical cancer, SLN biopsy had very high sensitivity and negative predictive value. We believe it is time to change the standard of care for women with early-stage cervical cancer to SLN biopsy only.

Introduction

For women with early-stage cervical cancer (stages IA1-IB1), the pathologic status of the lymph nodes is one of the most important prognostic factors and guides postoperative adjuvant therapy [1]. For that reason, complete pelvic lymphadenectomy together with radical hysterectomy or radical trachelectomy remains the standard of care for women with this disease. However, the incidence of nodal metastases in women with early-stage cervical cancer is only 15%–20% [2–4], meaning that 80%–85% of patients undergo an unnecessary complete pelvic lymphadenectomy, a procedure associated with increased blood loss, neurovascular and ureteral injuries, infections, lymphedema, lymphocyst formation, and venous thromboembolism [5].

In an effort to decrease the number of patients undergoing complete lymphadenectomy and thereby decrease complications from this procedure, lymphatic mapping and sentinel lymph node (SLN) biopsy has been established as standard in multiple solid tumor sites [6–8]. The earliest reports of use of this technique in patients with early-stage cervical cancer date to the 1990s [9]. Since then, lymphatic mapping and SLN biopsy in patients with cervical cancer has been evaluated in both single-institution experiences and multi-institutional prospective trials, which have collectively shown that in well-selected patients, the sensitivity may be > 99% [10].

In most gynecologic oncology practices, including our own, complete pelvic lymphadenectomy remains the standard procedure for assessing lymph node status in women with early-stage cervical cancer. However, for many years, we have been performing lymphatic mapping and SLN biopsy followed by complete pelvic lymphadenectomy as part of our surgical approach for women with early-stage cervical cancer. Initially, we performed lymphatic mapping and SLN biopsy to gain experience with and expertise in the procedure. Later, we realized that we were detecting more metastatic disease in lymph nodes through the ultrastaging and immunohistochemistry processing [11]. Now, we are contemplating abandoning complete lymphadenectomy for lymphatic mapping and SLN biopsy only. The objective of this study was to determine the sensitivity and negative predictive value of lymphatic mapping and SLN biopsy in women with early-stage cervical cancer and to identify demographic and/or tumor factors that may affect our ability to accurately identify SLNs in these patients.

Methods

After approval was obtained from the Institutional Review Board of The University of Texas MD Anderson Cancer Center, we performed a retrospective study of all patients diagnosed with early-stage cervical cancer (stages IA1-IB1 and IIA1) who underwent lymphatic

mapping and SLN biopsy followed by complete pelvic lymphadenectomy as part of primary treatment for their disease during the period from August 1997 through October 2015. Surgeries were performed via laparotomy, laparoscopy, or robotic approach by 18 different surgeons in our group. Lymphatic mapping was performed using technetium-99m sulfur colloid, patent blue dye, indocyanine green, or a combination of tracers. Tracers were injected superficially in four quadrants just lateral to the primary lesion (when visible) in equal aliquots at the 3-o'clock, 6-o'clock, 9-o'clock, and 12-o'clock positions. Patients were considered evaluable if sentinel lymph node mapping was attempted (i.e. dye was injected and nodal beds were reviewed) and a full lymphadenectomy was performed.

Intraoperatively, the retroperitoneum was opened, and lymph node basins were closely examined. Any lymph nodes with findings suggestive of metastatic disease were resected and sent for frozen section pathologic analysis. SLNs were then identified utilizing technetium Tc 99m and a gamma probe, indocyanine green and near-infrared imaging, blue dye and plain vision, or a combination of these techniques. SLNs were removed, labeled as such, and processed for examination of permanent sections. SLNs were not routinely sent for frozen section analysis unless there was evidence of metastatic disease on gross inspection. If results of frozen section analysis showed metastatic disease in any node (sentinel or grossly abnormal), lymphadenectomy was abandoned in favor of definitive chemoradiation therapy. For patients without metastasis detected on analysis of frozen sections, complete bilateral pelvic lymphadenectomy was performed after removal of the SLNs.

All surgical specimens were examined by pathologists specializing in gynecologic pathology. Ultrastaging was performed on all SLNs negative on hematoxylin-eosin staining. SLNs were considered positive for metastasis if they contained a macrometastasis (deposit > 2 mm), a micrometastasis (deposit 0.2 mm to 2 mm), or isolated tumor cells (microscopic clusters and single cells of carcinoma < 0.2 mm). Non-sentinel nodes were bivalved and stained with hematoxylin-eosin only.

Demographics and patient characteristics were analyzed, including age, body mass index (BMI), prior conization (cold knife cone biopsy or loop electrosurgical excision procedure), stage, grade, histology, depth of invasion, lymphovascular space invasion, tumor size (no visible lesion, lesion < 2 cm, or lesion ≥ 2 cm), and surgical approach (laparotomy, laparoscopy, or robotic).

To evaluate the success of lymphatic mapping, different variables were evaluated, including the technique used for mapping, rate of detection of SLNs and bilateral SLNs, number of SLNs removed, location of SLNs, number of positive SLNs, size of SLN metastases (isolated tumor cells, micrometastases, or macrometastases), extracapsular extension, and location of positive SLNs. Sensitivity, negative predictive value, and false-negative rates were calculated per patient and per hemi-pelvis. We considered findings to be false negative when lymphatic mapping showed drainage to one or more SLNs in a hemi-pelvis, biopsy of the SLN(s) revealed no metastases, and the patient had at least one metastatic non-SLN. A positive non-SLN in a hemi-pelvis with no SLN identified on lymphatic mapping was not

considered to indicate a false-negative finding as our practice is to perform a complete pelvic lymphadenectomy in any such “unmapped” hemi-pelvis.

We used descriptive statistics to summarize demographic and clinical characteristics. We similarly summarized the lymphatic mapping variables of interest. We used logistic regression methods to model the probability of having any SLN detected and the probability of having bilateral SLNs detected. We fit a full model including several factors of interest (age, BMI, tumor size, mapping technique, lymphovascular space invasion, previous cone biopsy). We then used backward elimination to remove variables from the model until all remaining variables were statistically significant at the $p < 0.05$ level.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at MD Anderson [12]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC).

Results

From August 1997 to October 2015, 188 patients with early-stage cervical cancer underwent lymphatic mapping and SLN biopsy followed by complete pelvic lymphadenectomy as part of their primary therapy. Patient demographics and tumor factors are summarized in Table 1. The median BMI was 26.6 kg/m², and 115 patients (61%) had undergone prior cervical conization. Most patients had stage IA2 disease (34 patients; 18%) or stage IB1 disease (136 patients; 72%). Fifty-five patients (29%) had tumors ≥ 2 cm based on clinical examination. Surgeries were performed via laparotomy in 90 patients (48%), laparoscopy in 32 (17%), and robotic surgery in 66 (35%).

At least 1 SLN was identified in 170 patients (90%). Bilateral SLNs were found in 117 patients (62%). The median number of SLNs identified per patient was 3 (range, 1–18). Table 2 shows SLN detection and bilaterality rates by tracer utilized. There was no significant difference between tracers in rate of detection of SLNs or rate of detection of bilateral SLNs. The locations of all SLNs identified are shown in Table 3. The majority of SLNs (83%) were found in the pelvis along the iliac vessels or in the obturator space. Only four patients (2%) had an isolated SLN in the aortocaval region.

Thirty-five patients (19%) had metastatic disease in regional lymph nodes. Of those 35 patients, 28 had at least one sentinel lymph node detected in the same hemi-pelvis as the metastatic node. One patient had a negative sentinel node detected in the right hemi-pelvis but ultimately was found to have microscopic metastatic disease to a lymph node in the left hemi-pelvis that did not map. An additional patient had a sentinel node found in the right hemi-pelvis but microscopic metastatic disease was found in an ipsilateral parametrial node. We did not consider either of these patients as true false negative cases and they were not

included in the analysis for sensitivity and NPV. In the 28 patients where metastatic disease was found in a mapping hemi-pelvis, 27 had metastatic disease found in at least one SLN (35 SLNs total with disease). Of the 27 patients with positive SLNs, 21 (78%) had disease detected by H and E staining and 6 patients (22%) had disease detected by ultrastaging/immunohistochemistry. Five nodes (14%) had macrometastases, 14 (40%) had micrometastases, and three (9%) had isolated tumor cells. Thirteen SLNs with metastases (37%) did not have tumor volume reported. Of the 27 patients with SLNs positive for metastatic disease, eight (30%) also had disease in non-SLNs. All patients with disease detected by immunohistochemistry had disease limited to SLN only with no non-SLNs positive for disease. The one patient with false-negative findings on SLN biopsy was a patient with bilateral SLNs detected and a total of seven SLNs detected. On the left side, she had one SLN detected in the parametrium, one along the left external iliac vessels, and two along the left common iliac vessels. Both the parametrial SLN and the external iliac SLN were positive for metastatic disease. On the right side, she had three external iliac SLNs detected. All three were negative for metastatic disease; however, a right obturator node was positive for metastatic disease.

When calculated on a per-patient basis, the sensitivity of SLN biopsy was 96.4% (95% CI 79.8%–99.8%) and the negative predictive value was 99.3% (95% CI 95.6%–100.0%). When calculated by hemi-pelvis, the sensitivity of SLN biopsy was 98.1% (95% CI 88.4%–99.9%) and the negative predictive value was 99.6% (95% CI 97.3%–100.0%).

Table 4 shows how the odds ratios for rates of detection of SLNs and bilateral SLNs were affected by potential confounders. There were no differences in overall SLN detection rates by prior conization (done or not done), body mass index ($<$ or $> 30 \text{ kg/m}^2$), or tumor size ($<$ or $\geq 2 \text{ cm}$). For bilateral SLN detection rates, only BMI $> 30 \text{ kg/m}^2$ decreased the ability to detect bilateral SLNs (OR=0.49, 95% CI 0.26–0.94, $p=0.03$). There was also no difference in overall detection rates when comparing surgical approach (open 93%, laparoscopic 91%, and robotic 86%, $p=0.32$); nor were there differences in bilateral detection rates by approach (open 66%, laparoscopic 69%, robotic 55%, $p=0.28$).

Discussion

In this series of 188 patients with early-stage cervical cancer who underwent lymphatic mapping and SLN biopsy followed by complete pelvic lymphadenectomy, we were able to detect at least one SLN in 90% of the patients and bilateral SLNs in 62% of the patients. SLN detection rates did not differ by mapping substance (technetium99m sulfur colloid, blue dye, and/or indocyanine green), prior conization, BMI, tumor size, or surgeon experience. Patients with BMI $> 30 \text{ kg/m}^2$, however, were less likely to have bilateral SLNs detected. Most importantly, only one patient had negative SLNs but disease detected in other nodes in the same hemi-pelvis, resulting in an overall sensitivity of 96.4% and negative predictive value of 99.3% for lymphatic mapping and SLN biopsy in women with early-stage cervical cancer.

The high sensitivity and high negative predictive value in our experience has led us to discuss changing our practice from complete pelvic lymphadenectomy to only lymphatic

mapping and SLN biopsy for women with early-stage cervical cancer. Our results are similar to those of a recent meta-analysis of 44 studies encompassing 3931 patients that found an overall sensitivity of 94% for patients who underwent SLN biopsy with ultrastaging of specimens [10]. Our standard protocol for all SLNs in all gynecologic sites is to perform ultrastaging of SLNs and in doing so we found an additional 22% of node positive patients that would have been missed with H and E staining alone. The importance of ultrastaging of specimens is highlighted in the study by Tax et al [10], in which ultrastaging improved the sensitivity of the procedure from only 81% to 94%.

Although many believe that performing SLN biopsy only is safe for women with cervical cancer, the two largest prospective studies of SLN biopsy in cervical cancer produced contradictory findings, leading some to question whether the procedure should be adopted as standard. In the SENTICOL study, 139 cervical cancer patients with stage IA1-IB1 tumors underwent SLN biopsy followed by complete pelvic lymphadenectomy [13]. In this study, the authors reported a sensitivity of 92% and a negative predictive value of 98%. However, one of the two reported instances of false-negative findings was an instance in which a metastatic node was found in a hemi-pelvis in which lymphatic mapping identified no SLNs. Many would not consider that a failure of the SLN concept, and most current mapping algorithms would not consider that instance a true false negative [14]. If we make that assumption, the sensitivity in the SENTICOL study was actually 96%, and the negative predictive value was actually 99%. The results presented in this paper are virtually equivalent to those results.

A few years before publication of SENTICOL, the AGO Study Group published their findings in 507 patients enrolled at 18 centers across Germany and Austria [15]. In this, the largest prospective study of the SLN concept in cervical cancer, the investigators found a sensitivity of only 77%. The authors acknowledged that this sensitivity was too low to recommend adopting the procedure. However, many features of the study call into question whether the results are applicable to SLN biopsy as it is generally performed today. First, the study did not utilize ultrastaging. As discussed above, the addition of ultrastaging greatly improves the sensitivity of the procedure [10]. Second, there was no assessment of the learning curve or volume of cases performed at each of the 18 centers involved. Most reported cases of false-negatives on SLN biopsy at other tumor sites, such as vulva and breast, have occurred in the first few cases a surgeon performs [7, 16]. Our one false-negative case came from a surgeon with low volume and few completed cases at the time of the event. Finally, the AGO Study Group allowed for very large tumors in their cohort. In fact, 32% of patients enrolled had disease more advanced than stage IB2 [15]. Large tumors are difficult to accurately map, and false-negative findings on SLN biopsy in patients with large tumors are common [17]. In fact, when the AGO Study Group limited their analysis to patients with tumors ≤ 2 cm, the sensitivity of the procedure was 91%. In our study, very few patients with tumors > 4 cm were enrolled, which likely contributed to our high overall sensitivity.

As we had only one case with false-negative findings on SLN biopsy, it was impossible to evaluate how technical approach (mapping substance), patient factors (BMI, prior conization), or tumor characteristics (tumor size) may adversely affect sensitivity. We did,

however, analyze how those factors may affect SLN detection rates, both overall and bilateral, and we found on multivariate analysis that obesity/morbid obesity was associated with a lower rate of detection of bilateral SLNs. Similar decreases in sentinel node detection rates in obese women have been reported in both breast [18] and endometrial cancer patients. [19, 20] This is likely a result of the difficulty in directly identifying lymphatic channels in thick adipose tissue. Although the use of indocyanine green may increase detection rates in obese women as it allows for surgeons to “see through” adipose tissue, near infrared imaging technology can only achieve a penetration depth of 1 cm. [21] With such minimal penetration depth, identification of sentinel nodes using indocyanine green and near infrared imaging remains challenging in obese and morbidly obese women.

Although we detected at least one sentinel node in 90% of our patients with cervical cancer, we found bilateral nodes in only 62% of patients. While this is consistent with the bilateral detection rate of 60% reported in a recent, large meta-analysis of cervical cancer mapping studies [10], we had hoped for a better performance and are evaluating our approach in an effort to improve our technique. As shown in our results, obesity did adversely effect our bilateral detection rates. It would be convenient to lay blame for our low bilateral detection rate solely on our obese patient population, however in reality the median BMI for patients in this study was 26.6 kg/m² so our perception may be of a patient population more obese than it truly is. There is certainly a well-recognized learning curve to this procedure and in this study only 4 of the 18 surgeons who performed the procedure had completed > 10 cases. We believe as the entire group gains experience, the overall and bilateral detection rate will continue to improve. In addition, we have recently moved from utilizing blue dyes and/or radiocolloid as mapping agents to indocyanine green with near infrared imaging. The literature shows that this newer technology leads to higher bilateral detection rates of 78–86% bilateral detection rate. [22, 23] As we will never achieve a 100% bilateral detection rate, it is important to always perform a complete lymphadenectomy in any hemi-pelvis that does not map.

The National Comprehensive Cancer Network (NCCN) has included sentinel node biopsy only as an option in the surgical treatment of early stage cervical cancer but has also cautioned that a non-mapping hemi-pelvis must undergo complete side specific lymphadenectomy. [24] In addition to performing complete pelvic side specific lymphadenectomy in any non-mapping hemi-pelvis, the algorithm outlined in the NCCN guideline also includes removing any grossly positive lymph nodes regardless of mapping status and performing ultrastaging and immunohistochemistry on all sentinel nodes along with performing a radical hysterectomy for women with stage IA2/IB1 disease. [24] Applying this approach to our cohort would have identified 100% of the patients who required adjuvant radiation therapy for high risk disease. In other words, even those patients with false negative sentinel nodes would have had their extra-cervical disease detected and none would have been denied the recommended adjuvant radiation therapy for positive nodes.

We specifically evaluated those factors previously reported as predictors for poor mapping. Although differences did not reach significance, mapping with combined technetium-99m and blue dye and mapping with indocyanine green had a trend towards a higher detection of

SLNs and a trend towards a higher detection of bilateral SLNs than mapping with blue dye or radiocolloid alone (Table 2). These findings are similar to those of a review of the literature, which found overall detection rates of 84% for blue dye only and 96% for combined blue dye and technetium 99m. [25]. We believe that indocyanine green alone and combined blue dye and radiocolloid are better than blue dye or radiocolloid alone, but our sample size did not have sufficient power to detect a difference. In fact, we calculated that at the detection rates reported, it would take a study of more than 300 patients to show a statistical significance between the methods.

We did not find a difference in SLN detection rates based on tumor size. Rob et al [17] did an extensive literature review and found that for tumors < 2 cm, the SLN detection rate was 95% and the sensitivity was 100%, while for tumors > 2 cm, the SLN detection rate was only 80% and the sensitivity was 89%. Our rates may have been better than those because our practice, with some rare exceptions, is to limit surgery and lymphatic mapping to patients with tumors < 4 cm. In fact, 95% of patients included in this study had tumors < 4 cm. In many of the studies included in the Rob et al review [17], tumors > 4 cm were included. As mentioned above, in patients with large tumors, lymphatic mapping often fails to identify SLNs, and false-negative findings are more frequent [26]. This may be due to difficulty finding adequate injection sites or inability of mapping substances to reach nodes as a result of debris or tumor emboli clogging lymphatic channels.

The main limitation of the study is the retrospective nature of the analysis. The introduction of new techniques and technology over the 18 years from which patients were included may have introduced bias as changes occurred in surgical approach, mapping substances, and patient selection over that time. In addition, all procedures were performed at a single, large tertiary referral center. While 18 different surgeons participated in the study, some might argue that the patient population and the resources at a large cancer center may be different from those in a community setting.

When considering SLN mapping in the setting of cervical cancer, many questions or issues remain of critical relevance as we move forward in the field. These include the issue of the learning curve as we have yet to determine what is the appropriate number of cases needed in order to achieve high detection rates with low false-negative rates. In addition, discussion of whether parametrial sentinel nodes should be considered in the calculation of detection rates continues given that presumably this tissue is always removed in a routine radical hysterectomy and thus should not be considered clinically relevant. Some have advocated for performing frozen section on all SLN specimens however we believe the destruction of nodal tissue during the intraoperative pathologic processing and examination will ultimately compromise detection of metastatic disease on postoperative examination with ultrastaging/immunohistochemistry. As we move towards suggesting SLN alone in the setting of early-stage cervical cancer, we must be certain that we, in fact, do have nodal tissue in the sentinel node specimen. A prospective validation study (sentinel node biopsy followed by complete pelvic lymphadenectomy) is unlikely to be performed in today's funding climate. The Gynecologic Oncology Group had previously attempted such a study (GOG 206) but it was closed due to poor accrual. Since then, investigators have attempted to redesign and reopen a similar prospective validation study through the collaborative group with no success. There

is, however, a current phase III study comparing laparotomy to minimally invasive radical hysterectomy in women with cervical cancer that plans to accrue 740 patients. [27] A component of this study involves performing sentinel lymph node biopsy followed by complete lymphadenectomy so additional prospective validation data on the procedure will be forthcoming.

In conclusion, in our series, we found a high sensitivity and negative predictive value for lymphatic mapping and SLN biopsy in women with early-stage cervical cancer. We believe it is reasonable to use this technique in place of complete lymphadenectomy; such a practice change could lead to decreased rates of complications such as vascular injuries, lymphocyst formation, and lymphedema as well as to higher rates of detection of nodal metastases because of ultrastaging's ability to find smaller nodal deposits. It is exceedingly unlikely that a prospective, randomized study comparing lymphatic mapping and SLN biopsy against complete pelvic lymphadenectomy will ever be performed; however, we believe the data we report herein as well as data from other retrospective and prospective studies successfully argue for adopting lymphatic mapping and SLN biopsy alone as the standard approach to evaluation of regional lymph nodes in women with early-stage cervical cancer.

Acknowledgments

Supported by the NIH/NCI under award number P30CA016672

References

- Fuller AF Jr, Elliott N, Kosloff C, Hoskins WJ, Lewis JL Jr. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. *Gynecol Oncol*. 1989; 33:34–9. [PubMed: 2703164]
- Diaz JP, Sonoda Y, Leitaio MM, Zivanovic O, Brown CL, Chi DS, Barakat RR, Abu-Rustum NR. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. *Gynecol Oncol*. 2008; 111:255–60. [PubMed: 18755500]
- Delgado G, Bundy BN, Fowler WC Jr, Stehman FB, Sevin B, Creasman WT, Major F, DiSaia P, Zaino R. A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 1989; 35:314–20. [PubMed: 2599466]
- Frumovitz M, dos Reis R, Sun CC, Milam MR, Bevers MW, Brown J, Slomovitz BM, Ramirez PT. Comparison of total laparoscopic and abdominal radical hysterectomy for patients with early-stage cervical cancer. *Obstet Gynecol*. 2007; 110:96–102. [PubMed: 17601902]
- 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]
- Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, Feldman S, Kusminsky R, Gadd M, Kuhn J, Harlow S, Beitsch P. The sentinel node in breast cancer--a multicenter validation study. *N Engl J Med*. 1998; 339:941–6. [PubMed: 9753708]
- Levenback CF, Ali S, Coleman RL, Gold MA, Fowler JM, Judson PL, Bell MC, De Geest K, Spirtos NM, Potkul RK, Leitaio MM Jr, Bakkum-Gamez JN, Rossi EC, Lentz SS, Burke JJ 2nd, Van Le L, Trimble CL. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. *J Clin Oncol*. 2012; 30:3786–91. [PubMed: 22753905]
- Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Wang HJ. Multicenter Selective Lymphadenectomy Trial G. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity

in MSLT-I, an international multicenter trial. *Ann Surg.* 2005; 242:302–11. discussion 311–3. [PubMed: 16135917]

9. Echt ML, Finan MA, Hoffman MS, Kline RC, Roberts WS, Fiorica JV. Detection of sentinel lymph nodes with lymphazurin in cervical, uterine, and vulvar malignancies. *South Med J.* 1999; 92:204–8. [PubMed: 10071668]
10. Tax C, Rovers MM, de Graaf C, Zusterzeel PL, Bekkers RL. The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review. *Gynecol Oncol.* 2015; 139:559–67. [PubMed: 26416173]
11. 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]
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42:377–81. [PubMed: 18929686]
13. 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]
14. 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]
15. Altgassen C, Hertel H, Brandstadt A, Kohler C, Durst M, Schneider A, Group AGOS. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. *J Clin Oncol.* 2008; 26:2943–51. [PubMed: 18565880]
16. East JM, Valentine CS, Kanchev E, Blake GO. Sentinel lymph node biopsy for breast cancer using methylene blue dye manifests a short learning curve among experienced surgeons: a prospective tabular cumulative sum (CUSUM) analysis. *BMC Surg.* 2009; 9:2. [PubMed: 19173714]
17. Rob L, Robova H, Halaska MJ, Hruda M, Skapa P. Current status of sentinel lymph node mapping in the management of cervical cancer. *Expert Rev Anticancer Ther.* 2013; 13:861–70. [PubMed: 23875664]
18. Derossis AM, Fey JV, Cody HS 3rd, Borgen PI. Obesity influences outcome of sentinel lymph node biopsy in early-stage breast cancer. *J Am Coll Surg.* 2003; 197:896–901. [PubMed: 14644276]
19. Tanner EJ, Sinno AK, Stone RL, Levinson KL, Long KC, Fader AN. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. *Gynecol Oncol.* 2015; 138:542–7. [PubMed: 26095896]
20. Eriksson AG, Montovano M, Beavis A, Soslow RA, Zhou Q, Abu-Rustum NR, Gardner GJ, Zivanovic O, Barakat RR, Brown CL, Levine DA, Sonoda Y, Leitao MM Jr, Jewell EL. Impact of Obesity on Sentinel Lymph Node Mapping in Patients with Newly Diagnosed Uterine Cancer Undergoing Robotic Surgery. *Ann Surg Oncol.* 2016; 23:2522–8. [PubMed: 26905542]
21. Schols RM, Connell NJ, Stassen LP. Near-infrared fluorescence imaging for real-time intraoperative anatomical guidance in minimally invasive surgery: a systematic review of the literature. *World J Surg.* 2015; 39:1069–79. [PubMed: 25522896]
22. Buda A, Bussi B, Di Martino G, Di Lorenzo P, Palazzi S, Grassi T, Milani R. Sentinel Lymph Node Mapping With Near-Infrared Fluorescent Imaging Using Indocyanine Green: A New Tool for Laparoscopic Platform in Patients With Endometrial and Cervical Cancer. *J Minim Invasive Gynecol.* 2016; 23:265–9. [PubMed: 26455525]
23. Hagen B, Valla M, Aune G, Ravlo M, Abusland AB, Araya E, Sundset M, Tingulstad S. Indocyanine green fluorescence imaging of lymph nodes during robotic-assisted laparoscopic operation for endometrial cancer. A prospective validation study using a sentinel lymph node surgical algorithm. *Gynecol Oncol.* 2016; 143:479–483. [PubMed: 27776838]
24. National Comprehensive Cancer Network. [Accessed January 30, 2017] Cervical Cancer (Version 1.2017). https://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf

25. Frumovitz M, Levenback CF. Lymphatic mapping and sentinel node biopsy in vulvar, vaginal, and cervical cancers. *Oncology (Williston Park)*. 2008; 22:529–36. discussion 538–9, 542–3. [PubMed: 18533402]
26. Zarganis P, Kondi-Pafiti A, Arapantoni-Dadioti P, Trivizaki E, Velentzas K, Vorgias G, Fotiou S. The sentinel node in cervical cancer patients: role of tumor size and invasion of lymphatic vascular space. *In Vivo*. 2009; 23:469–73. [PubMed: 19454516]
27. Obermair A, Gebiski V, Frumovitz M, Soliman PT, Schmeler KM, Levenback C, Ramirez PT. A phase III randomized clinical trial comparing laparoscopic or robotic radical hysterectomy with abdominal radical hysterectomy in patients with early stage cervical cancer. *J Minim Invasive Gynecol*. 2008; 15:584–8. [PubMed: 18722970]

Highlights

- Sentinel lymph node biopsy alone has a sensitivity of 96.4% in detecting metastatic disease in early stage cervical cancer
- Sentinel lymph node biopsy alone has a negative predictive value of 99.3% in early stage cervical cancer
- SLN biopsy alone is a valid procedure and should be considered for women with early stage cervical cancer

Table 1

Demographics and tumor factors

Age, median (range), yr	38 (21–68)
Body mass index, median (range), kg/m ²	26.6 (15.9–47.8)
Surgical approach, n (%)	
Laparotomy	90 (48)
Laparoscopy	32 (17)
Robotic	66 (35)
Histology, n (%)	
Squamous carcinoma	95 (50)
Adenocarcinoma	65 (35)
Adenosquamous carcinoma	15 (8)
Non-squamous, non-adenocarcinoma	13 (7)
Grade, n (%)	
1	22 (11.7)
2	90 (47.9)
3	67 (35.6)
Unknown	9 (4.8)
Lymphovascular space invasion, n (%)	
Yes	67 (36)
No	56 (30)
Unknown	65 (34)
Depth of invasion, median (range), mm	3.5 (0–18)
Tumor size, median (range), mm	30 (0–60)
Tumor ≥ 2 cm, n (%)	
Yes	55 (29)
No	133 (71)
Stage, n (%)	
IA1	13 (6.9)
IA2	34 (18)
IB1	136 (72)
IB2	3 (1.6)
IIA1	2 (1.1)
Prior conization/LEEP, n (%)	
Yes	115 (61)
No	73 (39)

Table 2

Rates of detection of sentinel lymph nodes (SLNs) and bilateral SLNs by tracer(s) utilized

Tracer	Rate of detection of SLNs (s), %	Rate of detection of bilateral SLNs, %	<i>p</i> value
Any tracer type (complete cohort; n=188)	90	62	
Single Modality ¹ (n=31)	84	55	NS
Combined ² (n=101)	93	67	NS
Indocyanine green (n=56)	89	57	NS

¹Single modality was either blue dye alone (n=29) or technecium-99 alone (n=2)²Combine modalities was blue dye and tecnecium-99

NS – not statistically significant

Table 3

Location of sentinel lymph nodes (SLNs) (n=595) in women with early-stage cervical cancer

Location of SLNs (n=595)	N	%
Parametrial	25	4.2
Obturator/internal iliac	249	41.9
External iliac	188	31.6
Pelvic NOS	54	9.1
Common iliac	60	10.0
Presacral	5	0.8
Aortocal	14	2.4

NOS – not otherwise specified

Table 4

Logistic regression for factors affecting rates of detection of sentinel lymph nodes (SLNs) and bilateral SLNs

Factor	OR (95% CI)	
	Overall SLN detection	Bilateral SLN detection
Prior conization (versus no conization)	0.96 (0.3–3.0)	0.58 (0.27–1.20)
Body mass index > 30 kg/m ² (versus ≤ 30 kg/m ²)	1.89 (0.55–6.48)	0.49 (0.25–0.96)
Tumor ≤ 2 cm (versus > 2 cm)	0.42 (0.13–1.32)	0.90 (0.43–1.87)