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Sentinel Lymph Node Biopsy in the Management of Early-Stage Cervical Carcinoma

John P. Diaz, M.D.^{1,*}, Mary L. Gemignani, M.D.¹, Neeta Pandit-Taskar, M.D.², Kay J. Park, M.D.³, Melissa P. Murray, M.D.³, Dennis S. Chi, M.D.¹, Yukio Sonoda, M.D.¹, Richard R. Barakat, M.D.¹, and Nadeem R. Abu-Rustum, M.D.¹

¹Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

²Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY

³Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Objectives—We aimed to determine the sentinel lymph node detection rates, accuracy in predicting the status of lymph node metastasis, and if pathologic ultrastaging improves the detection of micrometastases and isolated tumor cells at the time of primary surgery for cervical cancer.

Methods—A prospective, non-randomized study of women with early-stage (FIGO stage IA1 with lymphovascular space involvement – IIA) cervical carcinoma was conducted from June 2003 to August 2009. All patients underwent an intraoperative intracervical blue dye injection. Patients who underwent a preoperative lymphoscintigraphy received a 99m Tc sulfur colloid injection in addition. All patients underwent sentinel lymph node (SLN) identification followed by a complete pelvic node and parametrial dissection. SLN were evaluated using our institutional protocol that included pathologic ultrastaging.

Results—SLN mapping was successful in 77 (95%) of 81 patients. A total of 316 SLN were identified, with a median of 3 SLN per patient (range, 0-10 SLN). The majority (85%) of SLN were located at three main sites: the external iliac (35%); internal iliac (30%); and obturator (20%). Positive lymph nodes (LN) were identified in 26 (32%) patients, including 21 patients with positive SLN. Fifteen of 21 patients (71%) had SLN metastasis detected on routine processing. SLN ultrastaging detected metastasis in an additional 6/21 patients (29%). Two patients had grossly positive LN at exploration, and mapping was abandoned. Three of 26 (12%) patients had successful SLN mapping; however, the SLN failed to identify the metastatic LN. Of these 3 false negative cases, 2 patients had a metastatic parametrial node as the only positive LN with multiple negative pelvic nodes including negative SLN. One patient with stage IA1 disease and

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Corresponding author: Nadeem R. Abu-Rustum, M.D. Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10065 Phone: 212.639.8125 Fax: 212.717.3214 gynbreast@mskcc.org.

*Currently at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

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lymphovascular invasion had unilateral SLN mapping and a metastatic common iliac LN identified on completion lymphadenectomy of the contralateral side that did not map. The 4 (5%) patients with unsuccessful mapping included 1 who had grossly positive nodes identified at the time of laparotomy; the remaining 3 occurred during each surgeon's initial SLN mapping learning phase.

Conclusion—SLN mapping in early-stage cervical carcinoma yields high detection rates. Ultrastaging improves micrometastasis detection. Parametrectomy and side-specific lymphadenectomy (in cases of failed mapping) remain important components of the surgical management of select cases.

Keywords

Sentinel lymph nodes; micrometastasis; cervical cancer

Introduction

Cervical carcinoma is the third most common gynecologic malignancy in the United States (1). Radical hysterectomy and pelvic lymphadenectomy are the standard surgical treatments for patients with early-stage cervical cancer (2-4). The most important prognostic factor in early stage cervical carcinoma is the presence or absence of metastatic carcinoma in the pelvic lymph nodes (5-6). The reported incidence of nodal metastases ranges from 0% to 31% for patients with IB carcinoma and less than 15% in patients with tumors ≤ 2 cm in size (4,5,7). The majority of patients with early-stage cervical carcinoma will not benefit from a pelvic lymphadenectomy. This cannot be ignored as most complications in surgical treatment of cervical cancer are related to parametrectomy and lymphadenectomy (8-10).

Over the last decade the sentinel lymph node (SLN) procedure has been widely used in patients with melanoma, breast and vulvar carcinomas (11,12,13). The clinical benefits of SLN biopsy include reduced relative risk of lymphedema and sensory loss (14). Benefits specific to the management of cervical cancer include a decrease in nerve, great vessel, and ureteral injuries, reduced blood loss and operative time, increased identification of metastatic lymph nodes through ultrastaging, and identification of alternate lymphatic drainage sites (7,15). The feasibility of SLN identification in cervical carcinoma has been well documented.

This cohort study demonstrates a single institution experience with sentinel lymph node biopsy in the management of early-stage cervical carcinoma. The objective is to demonstrate the viability of implementing a SLN program using the combination of blue dye and lymphoscintigraphy techniques and the potential pitfalls of SLN biopsy in cervical carcinoma. In addition to the surgical aspect of SLN biopsy we demonstrate the benefits of pathologic ultrastaging of SLNs.

Methods

Between June 2003 and August 2009, SLN mapping was performed in 81 patients for whom a radical surgery for early-stage cervical cancer had been planned. All patients signed informed consent. In the early phase of the study a combination of preoperative technetium-99 (99m Tc) sulfur colloid injection and lymphoscintigraphy with intraoperative blue dye injection was utilized. As we became more experienced in identifying the SLN, the preoperative 99m Tc sulfur colloid injection and lymphoscintigraphy were discontinued in favor of only intraoperative blue dye injection.

Preoperative lymphoscintigraphy

Preoperative lymphoscintigraphy was performed using technetium-99. The Tc-99 was injected superficially at the periphery of the tumor, in the four quadrants of the cervix using a 25 gauge spinal needle. The injection was done under direct visualization without the need for colposcopic guidance. The injection was performed the day prior to surgery and an anterior lymphoscintigram with a posterior transmission flood was done about 1 hour after the injection. The lymphoscintigram were reviewed by an attending radiologist in addition to the attending surgeon. They were always available in the operating room to assist in the identification of the SLN.

Intraoperative lymphatic mapping

After induction of general anesthesia, the isosulfan blue dye (Lymphazurin 1%, US Surgical Co., Norwalk, CT) was injected under direct visualization into the four quadrants of the cervix using a 25-gauge spinal needle. Care was taken to inject slowly and superficially into the stroma of the cervix. After our initial experience we modified our intracervical injection sites. One mL of blue dye is injected deep and 1 mL is injected superficially at the 3 o'clock and 9 o'clock sites, for a total of 4 mL.

Sentinel node identification

The retroperitoneum was accessed in the standard fashion with care to avoid bleeding from vessels and capillaries which may stain the retroperitoneum resulting in greater difficulty in identifying the blue lymphatic channels. Once identified the blue lymphatic channels were followed all the way to their ending blue lymph node, which was considered the SLN. If a preoperative lymphoscintigraphy had been performed, then before removing the SLN a gamma probe was utilized to obtain counts. Counts were first obtained at the level of the cervix and then counts were obtained on the blue node and recorded. The node was then removed and counts were done again on the node and nodal bed for confirmation. A thorough surgical exploration of the retroperitoneum was then performed for any palpably enlarged lymph nodes. A completion pelvic lymphadenectomy was then performed on all patients.

For patients undergoing a fertility-sparing radical trachelectomy, all SLN were sent for frozen section analysis. In addition any enlarged lymph nodes (LN) were also sent for frozen section analysis. In the event of metastatic disease on frozen section analysis of SLN or suspicious node it was at the discretion of the attending physician as to perform a paraaortic LN dissection and/or perform a completion radical hysterectomy.

A successful sentinel lymph node mapping was defined as identification of at least one sentinel lymph node. A sentinel lymph node was defined as any lymph node identified through the use of blue dye injection, 99m Tc injection, or a combination of both techniques. In addition any grossly enlarged lymph node in the absence of blue dye or a 99 Tc uptake was considered a sentinel lymph node. The absence of a lymph node identified by blue dye and/or radioactive uptake was documented as a failed sentinel lymph node mapping. Any patient who underwent a successful sentinel lymph node mapping and was subsequently discovered to have a metastatic non-sentinel lymph node was defined as a false negative sentinel lymph node.

Pathologic Evaluation

The pathology protocol for SLN evaluation at our institution is as follows: from each paraffin block lacking metastatic carcinoma appreciable in a routine section stained with hematoxylin and eosin (H&E), 2 adjacent 5- μ m sections were cut at each of two levels 50 μ m apart. At each level, one slide was stained with H&E and the other with

immunohistochemistry (IHC) using the anti-cytokeratin AE1:AE3, as well as one negative control slide, for a total of 5 slides per block. Micrometastasis was defined as a focus of metastatic cancer ranging from 0.2 mm to no more than 2 mm. Isolated tumor cells were defined as metastasis measuring no more than 0.2 mm, including the presence of single non-cohesive cytokeratin-positive tumor cells.

Results

A total of 81 patients underwent SLN biopsy followed by completion lymphadenectomy between June 2003 and August 2009. The patient demographics and tumor characteristics are described in Table 1. The following surgical procedures were performed: 48 (59%) patients underwent a radical hysterectomy; 29 (36%) underwent a fertility-sparing radical trachelectomy; 3 (4%) underwent a cold knife conization; 1 (1%) an aborted radical hysterectomy.

Sentinel lymph node mapping was successful in 77 (95%) of patients (Table 2), with an overall sensitivity of detecting metastatic disease of 88%. The false negative rate was 12%. The overall negative predictive value (NPV) was 95%, Figure 1. The false negative predictive value is 0.05. A total of 316 SLN were identified with a median of 3 SLN per patient (range 0 – 10, SLN). The majority (85%) of SLN were located in the three main sites: the external iliac (35%), internal iliac (30%), and obturator (20%), Figure 2. Positive lymph nodes were identified in 26 (32%) patients. Two patients had grossly positive lymph nodes at exploration and mapping was abandoned. Three of 26 (12%) patients had successful SLN mapping; however, the SLN failed to identify the metastatic lymph nodes. Of these 3 false negative cases, 2 patients had a metastatic parametrial node as the only positive lymph nodes with multiple negative pelvic nodes including negative SLN. One patient with stage IA1 disease and lymphovascular invasion had unilateral SLN mapping and a metastatic common iliac lymph node identified on completion lymphadenectomy of the contralateral side that did not map, Figure 3.

The 2 patients with false negative pelvic SLN due to positive parametrial lymph nodes had similar tumor characteristics. Both were stage IB1 with no gross lesion. They were of squamous histology, with deep stromal invasion and evidence of lymphovascular space invasion. However, neither patient would have met criteria for adjuvant therapy based on these local tumor findings alone.

Positive sentinel lymph nodes were identified in 21/77 (27%) patients with a total of 27 positive SLN and a median positive SLN of 1 per patient (range, 1-2, positive SLN). The positive SLN locations include: 12 (44%) external iliac, 8 (30%) internal iliac, 6 (22%) obturator and 1 (4%) parametrial. Fifteen (71%) patients had SLN metastases detected by routine processing. Moreover, SLN ultrastaging detected metastasis in an additional 6/21 (29%) patients. Of these patients one had micrometastasis detected on additional hematoxylin and eosin (H & E) sections as required by our protocol. Five of 21 (24%) patients had isolated tumor cell metastasis detected by immunohistochemistry. All of the patients with positive SLN are currently alive.

Thirty-four (42%) patients underwent an attempt at fertility-sparing surgery for early-stage cervical carcinoma. During this period we submitted all SLN identified in these patients for frozen section analysis of metastatic disease. Overall 13/34 (38%) patients had positive lymph nodes. One patient had a grossly enlarged lymph node with metastasis on frozen section. Another patient only had unilateral SLN mapping and a metastatic common iliac lymph node identified on completion lymphadenectomy of the contralateral side that did not map. All remaining 32 patients had successful SLN mapping. Only 2 (6%) of 32 patients

had positive non-suspicious SLNs on frozen section. On final pathology, an additional 7 (22%) of 32 cases had positive SLNs. Of those 7 cases, 4 were detected only on ultrastaging protocol. Two additional patients had a metastatic parametrial lymph node in the trachelectomy specimen as the only positive lymph node with negative pelvic lymph nodes. Routine intraoperative frozen section of SLN in combination with frozen-section analysis of grossly enlarged nodes altered the intraoperative management of 9% of patients undergoing a fertility-sparing surgical procedure.

Discussion

We continue to search for a surgical technique that provides accurate pathologic information about the nodal status of patients with early-stage cervical carcinoma without overtreating potentially low-risk patients and undertreating patients with metastatic disease. SLN mapping has been widely adapted in the management breast, melanoma, and vulvar cancer. SLN may provide the solution to the complicated issue of minimizing surgical morbidity while maximizing the pathologic information of nodal status in these patients.

The feasibility of SLN identification in cervical carcinoma has been well document (7,16-19). Nearly 800 patients with cervical cancer have undergone SLN mapping in the reported literature. The SLN detection rate was 90% with an overall rate of metastatic disease of 21% in these studies. The sensitivity, defined as the detection of metastatic disease in the SLN when there actually is metastatic disease in the nodal basin, is 92%. This translates into <8% of patients undergoing sentinel node detection will be falsely-negative meaning that metastatic disease in the lymph nodes is present yet the sentinel node is negative for metastatic disease. The negative predictive value in the combined literature is 97%, (7, 16-19). Our findings are consistent with those reported in the literature and support the achievability and accuracy of SLN mapping.

One of the potential benefits of SLN mapping is a reduction in the morbidity of the surgical management of early-stage cervical cancer. In an effort to further reduce the morbidity some have investigated eliminating the parametrectomy in patients with negative SLN (20, 21). Retrospective studies have demonstrated that the incidence of parametrial involvement is very low in the subgroup of patients with a tumor size ≤ 2 cm in diameter, less than 10 mm of invasion, and negative lymph nodes (22-26). The group from Charles University Prague has reported their initial experience of 60 patients with favorable cervical tumors (stage IA1 with lymphovascular space invasion through IB1 with tumor size < 20 mm and less than half stromal invasion based on MRI and ultrasound), who underwent a laparoscopic SLN mapping with frozen section and simple vaginal hysterectomy (21). In their series all node positive patients were with SLN positive only. No false negative SLNs were noted in any of the 60 patients. Two false negative frozen section results were observed. In both cases it was micrometastasis less than 2 mm that was detected by serial sectioning of the SLNs. There were no recurrences in 55 SLN negative patients and in 5 SLN positive patients. The authors concluded that it is both feasible and safe to reduce the radicality of parametrial resection for small tumor volume in SLN negative patients.

The authors are recognized for their expertise in the management of cervical cancer and SLN mapping. However, based on our own experience we are cautious to adapt these guidelines at this time. In our series 7/32 patients with negative SLN on frozen section had evidence of metastatic disease on final pathology. Four of the 7 were identified with our ultrastaging protocol. In addition, 8% of all node positive cases were due to microscopic parametrial nodal metastasis. These patients all received adjuvant therapy. Had these patients undergone a simple hysterectomy based upon negative SLN, their metastatic disease would have gone undiagnosed and they would have been undertreated. Identifying

parametrial SLN is challenging even with combined blue dye and 99m Tc sulfur colloid. Based on our own findings we continue to routinely include parametrectomy in the surgical management of these patients. Exceptions have been made in highly select patients. In our cohort, three patients with stage IA1, "microinvasive disease," and lymphovascular space involvement (LVS) on initial conization were offered fertility-sparing cold knife conization in conjunction with sentinel lymph node mapping and completion lymphadenectomy. All patients had successful SLN mapping with no evidence of metastasis. There was no residual tumor on all three conization specimens. All patients are alive and well with no evidence of recurrence at time of last follow up.

The frequency of micrometastases (MM) in gynecologic and non-gynecologic malignancies ranges from 8%-20.7% (27-29). In surgically treated cervical cancer patients with and without the use of sentinel lymph node (SLN) technique, a mean frequency of 12.9% (3.8-23.9%) for MM has been reported (30-34). The rate of MM and or isolated tumor cells (ITC) in our series was 8%. The clinical relevance of these findings is not yet fully understood. Dutch investigators compared over 2700 patients with breast cancer: 856 patients with node-negative disease who did not receive any systemic adjuvant therapy; 856 patients with ITC or MM who did not received any systemic adjuvant therapy; and 995 patients with ITC or MM who did receive adjuvant systemic therapy (35). The 5-year rate of disease-free survival among women with ITC or MM who did not received adjuvant therapy was significantly reduced compared with the rate of the node-negative, no adjuvant therapy cohort. Additionally, the 5-year rate of disease-free survival among women with ITC or MM who did not receive adjuvant therapy was significantly reduced compared with the rate of ITC or MM who did receive adjuvant therapy. Horn et al. evaluated 894 patients with state I-IIb cervical carcinoma for evidence of MM and compared their recurrence-free survival to node negative patients. Patients with macro and micrometastasis represented a significant reduced RFS compared to those with node negative disease (15). The authors from this study concluded that micrometastatic disease represents an independent prognostic factor and may be candidates for adjuvant therapy. There is currently no data in cervical carcinoma that reports outcome of patients with ITC or MM who received adjuvant therapy. At this time we do not routinely offer adjuvant therapy to patients with evidence of MM or ITC. None of these patients have recurred.

SLN mapping in cervical cancer has been well described in the literature; yet, the total number of node-positive cervical cancer patients reported in the literature is still too small to change practice standards. Our series is consistent with previous findings and adds to the growing body of literature, confirming the feasibility of performing SLN mapping in this disease. Routine intraoperative frozen section of SLNs in combination with frozen-section analysis of grossly enlarged nodes altered the intraoperative manage of 9% of patients undergoing fertility-sparing surgery. Permanent pathologic evaluations of SLNs with ultrastaging yields a considerable number of additional positive SLN cases, which will likely change adjuvant treatment plans and ultimately affect fertility preservation. Although frozen section of SLNs may help in intraoperative decision making, these data suggest that its usefulness has limitations. Parametrectomy remains an important component of the surgical treatment since nearly 8% of node positive cases were due to microscopic parametrial nodal metastasis. Pathologic ultrastaging of SLN yielded an additional 22% of node-positive cases. The clinical impact of these findings is not yet fully understood. Some studies suggested these patients may have a worse outcome and may potentially benefit from systemic adjuvant therapy. The growing body of literature supports the incorporation of SLN mapping in the management of early-stage disease cervical carcinoma. We must move beyond simply identifying a blue or hot node at the time of surgery. Instead we must incorporate a systematic sentinel lymph node algorithm to the management of early-stage cervical cancer. This algorithm should incorporate removal of any visible suspicious/gross

disease, requirement for bilateral parametrectomy in conjunction with resection of the primary tumor and side-specific lymphadenectomy (including the inter iliac or subaortic nodes) in cases where only unilateral SLN mapping is achieved, Figure 4.

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Research Highlights

- SNL mapping in early-stage cervical carcinoma yields high detection rates.
- Ultrastaging improves micrometastasis detection.

		Metastatic Lymph Node		Total
		Positive	Negative	
Sentinel Lymph Node	Positive	23	0	23
	Negative	3	55	58
	Total	26	55	

Sensitivity	88%	PPV	100%
Specificity	100%	NPV	95%

Figure 1. Diagnostic Test of Sentinel Lymph Node

A total of 26 patients had evidence of metastatic lymph nodes on final pathology. Twenty-one patients had a metastatic sentinel lymph node (SLN). An additional 2 patients had grossly enlarged lymph nodes that were included in this analysis as sentinel lymph nodes. Two additional patients had successful SLN mapping; however failed to identify the metastatic parametrial lymph node. One additional patient had unilateral SLN mapping and a metastatic lymph node identified on the contralateral side.

Figure 2. Location of Sentinel Lymph Nodes

The majority (85%) of SLN were located at three main sites: the external iliac (35%); internal iliac (30%); and obturator (20%).

Figure 3.
Metastatic pelvic lymph nodes.

Figure 4.
Suggested Sentinel Lymph Node Algorithm

Table 1

Demographics and Tumor Characteristics, N = 81

Variable	N (%)
Age	
Median (range)	36 (15-68)
Ethnicity	
White	73 (90)
Hispanic	7 (9)
Other	1 (1)
Stage	
IA1	8 (10)
IA2	4 (5)
IB1	64 (79)
IB2	4 (5)
IIA	1 (1)
Histology	
Squamous	28 (34)
Adenocarcinoma	53 (65)
Lymph node status	
Positive	26 (32)
SLN positive	21 (26)
Negative	55 (68)
BMI	
Median (range)	23.8 (17.7-45.0)

SLN, sentinel lymph nodes; BMI, body mass index

Table 2

Sentinel Lymph Node Mapping Detection, N = 81

Variable	99m TC and Blue Dye N = 63, N (%)	Blue Dye Only N = 18, N (%)	All Patients N = 81, N (%)
Successful SLN Identification			
Per Patient	60 (95)	17 (94)	77 (95)
Per Side			
Right Side	55 (87)	14 (78)	69 (85)
Left Side	52 (83)	14 (78)	66 (81)
Bilateral	47 (75)	11 (61)	58 (72)

99m Tc, technetium-99 sulfur colloid; SLN, sentinel lymph node