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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], Michael Frumovitz [a,*]

[a] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States
[b] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States
[c] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States

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

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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-99 m 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/m^2 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 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.

1. 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].

* Corresponding author at: Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, 1155 Pressler St., Unit 1362, Houston, TX 77030, United States.
E-mail address: mfrumovitz@mdanderson.org (M. Frumovitz).

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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.

2. 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 99 m 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 99 m 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).

3. 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/m^2, 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

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