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The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes ☆

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ABSTRACT

Objective. To determine the false-negative rate of a surgical sentinel lymph node (SLN) mapping algorithm that incorporates more than just removing SLNs in detecting metastatic endometrial cancer.

Methods. A prospective database of all patients who underwent lymphatic mapping for endometrial cancer was reviewed. Cervical injection of blue dye was used in all cases. The surgical algorithm is as follows: 1) peritoneal and serosal evaluation and washings; 2) retroperitoneal evaluation including excision of all mapped SLNs and suspicious nodes regardless of mapping; and 3) if there is no mapping on a hemi-pelvis, a side-specific pelvic, common iliac, and interiliac lymph node dissection (LND) is performed. Paraaortic LND is performed at the attendings' discretion. The algorithm was retrospectively applied.

Results. From 9/2005 to 4/2011, 498 patients received a blue dye cervical injection for SLN mapping. At least one LN was removed in 95% of cases (474/498); at least one SLN was identified in 81% (401/498). SLN correctly diagnosed 40/47 patients with nodal metastases who had at least one SLN mapped, resulting in a 15% false-negative rate. After applying the algorithm, the false-negative rate dropped to 2%. Only one patient, whose LN spread would not have been caught by the algorithm, had an isolated positive right paraaortic LN with a negative ipsilateral SLN and pelvic LND.

Conclusions. Satisfactory SLN mapping in endometrial cancer requires adherence to a surgical SLN algorithm and goes beyond just the removal of blue SLNs. Removal of any suspicious node along with side-specific lymphadenectomy for failed mapping are an integral part of this algorithm. Further validation of the false-negative rate of this algorithm is necessary.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with approximately 46,000 new cases and 8000 deaths in 2011 [1]. The revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system continues to incorporate lymph node (LN) status as it has been shown to be diagnostic and prognostic [2,3], but there is continued controversy over the role of lymphadenectomy (LND) in endometrial cancer. The benefit of lymphadenectomy has been refuted by two recent randomized controlled trials that did not demonstrate a therapeutic benefit to lymphadenectomy itself, although the methodology of both studies has been criticized [4,5]. A Study in the Treatment of Endometrial Cancer (ASTEC) was a large multicenter study in which almost half of the patients randomized to the LND arm had ≤9 LNs removed, and in addition, many patients were secondarily randomized to postoperative radiation independent of LN status [5]. The trial by Panici et al. did require a minimum of 20 LNs removed, but adjuvant treatment was given at the discretion of the physician and was similar in the two groups [4]. Even for those who agree that LND is not therapeutic, many still argue that LN staging is essential to guide appropriate adjuvant therapy. It is not surprising then that a survey of Society of Gynecologic Oncology (SGO) members conducted in 2009 demonstrated a lack of standardized surgical practice patterns of LND in endometrial cancer staging among providers [6].

Sentinel lymph node (SLN) mapping may serve as a potential middle ground in endometrial cancer surgical staging between no evaluation of LN status and a full pelvic and paraaortic LND as a way to adequately evaluate a patient's LN status while decreasing the risk of morbidity from a full LND, and overcoming the confusion of what the standard templates for LND are in this disease. SLN is a well-

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accepted practice in the treatment of melanoma and breast cancer [7,8] and is gaining ground in vulvar cancer [9] and cervical cancer [10]. A recent prospective multi-institutional study (SENTI-ENDO), using a similar technique of cervical injection to our approach, demonstrated that SLN biopsy may be a reasonable alternative in endometrial cancer staging [11]; this study confirmed similar and previously published observations from our institution [12,13].

The key to the controversy of LND in endometrial cancer is to agree upon a clinically practical, reproducible, and reliable method of evaluating LN status to guide prognosis and adjuvant treatment while minimizing morbidity from a procedure that is probably not in and of itself therapeutic. We propose an endometrial cancer SLN algorithm that goes beyond just removal of blue nodes. The objective was to determine the effectiveness of this algorithm in detecting metastatic endometrial cancer while minimizing the need for complete LND.

Methods

We reviewed the results of all patients from September 2005 through April 2011 who underwent SLN mapping as part of their surgery for endometrial cancer at Memorial Sloan-Kettering Cancer Center (MSKCC). Surgery was performed by laparoscopy, robotically assisted laparoscopy, or laparotomy. Surgical staging included total hysterectomy, bilateral salpingo-oophorectomy, and mapping of SLNs. The extent of bilateral pelvic and paraaortic LND was left to the operating surgeon's discretion.

All patients underwent blue dye injection into the cervix at the time of exam under anesthesia. The cervix was injected at the 3 and 9 o'clock positions with 1 mL superficial (2–3 mm) and 1 mL deep (1–2 cm), for a total of 4 mL. A small number of patients in the earlier part of the study received a blue dye injection into the fundus (1 mL into the anterior mid fundus and 1 mL into the posterior mid fundus) and/or a preoperative lymphoscintigraphy following a cervical injection of technetium-99 microsulfur colloid.

Beginning in 2005 we utilized both Tc and blue dye injection in the cervix. Following completion of our initial institutional clinical trial in 75 cases, we moved more in the direction of blue dye injection only into the cervix. All patients in this study had blue dye injected into the cervix. This is the easiest and most convenient injection site and avoids the need for a preoperative nuclear medicine injection and lymphoscintigram, which is associated with additional costs and discomfort (due to injecting the cervix with Tc when the patient is awake), and in our experience did not improve the detection rates. We do not claim that cervical injection of blue dye is superior to other methods, but from the standpoint of clinical feasibility, the performance of our algorithm can be interpreted knowing that the sensitivity, negative predictive value, and false-negative rate that we report were attained based upon the simplest of mapping protocols. Although there are no prospective randomized trials comparing injection site or detection method, a recent meta-analysis did find that the use of cervical injection was significantly associated with an increased detection rate, whereas hysteroscopic injection was associated with a decreased detection rate, and subserosal injection was associated with decreased sensitivity, thereby lending further support to our approach of cervical injection for SLN mapping [16].

SLNs were detected by direct visualization of blue dye or were localized using a gamma probe to detect hot nodes. Further detail on our mapping protocol was previously reported [14]. Grossly enlarged LNs were removed and properly documented in the surgeon's operative report; although these nodes if positive for disease are equivalents of SLN, for the purposes of this analysis, they were not considered SLNs unless they contained blue dye.

Specialized gynecologic pathologists examined all specimens. The MSKCC institutional protocol for evaluation of SLNs includes initial examination by routine hematoxylin and eosin (H&E) staining, followed by ultrastaging if the initial H&E is negative. Ultrastaging consists of two adjacent 5 μm sections cut from each paraffin block at each of two levels 50 μm apart, for a total of four slides per block. At each level, one slide is stained with H&E and the other with immunohistochemistry using anti-cytokeratin AE1:AE3 (Ventana Medical Systems, Inc., Tucson, AZ). SLNs were considered positive if they demonstrated macrometastasis (defined as tumor clusters > 2 mm), micrometastasis (defined as tumor clusters between 0.2 and 2 mm), or isolated tumor cells (ITCs) (defined as single tumor cells or small tumor clusters ≤ 0.2 mm) [15]. LNs containing only isolated cytokeratin-positive cells were not considered metastatic.

In order to determine the effectiveness of a surgical SLN mapping algorithm in detecting metastatic endometrial cancer while minimizing the need for complete LND, we performed descriptive statistics for SLN mapping alone compared to our proposed SLN algorithm. Each patient, rather than each hemipelvis, was used as the unit of analysis.

The SLN detection rate was defined as the proportion of cases in which at least one SLN was identified among patients with attempted mapping. Failed mapping refers to cases in which an SLN was not detected. Cases with bilateral failed mapping with no SLNs removed were considered non-evaluable for analysis of SLN alone; cases with no LNs taken (SLN or non-SLN) were considered non-evaluable for analysis of the algorithm. A true-negative was defined as a negative SLN or algorithm in a patient with no nodal metastases. A false-negative was a negative SLN or algorithm in a patient with nodal metastases. A true-positive was defined as a positive SLN or algorithm in a patient with nodal metastases, and a false-positive was impossible by definition. Sensitivity was calculated as the number of true positives divided by all patients with LN metastases. The false-negative rate was the number of false-negatives divided by the number of patients with LN metastases. Clinically, the false-negative rate refers to the detection of LN metastasis in the completion LND when an SLN was excised and pathologically benign. The negative predictive value was determined by dividing the number of true negatives by the number of patients with a negative test (SLN alone or algorithm).

We retrospectively applied the algorithm, as shown in Fig. 1, which includes the following steps: 1. peritoneal and serosal evaluation and washings; 2. retroperitoneal evaluation including excision of all mapped SLNs and removal of all suspicious nodes regardless of mapping; and 3. If there is no mapping on a hemipelvis, a side-specific pelvic (external iliac, internal iliac, and obturator), common iliac, and interiliac LND is performed. Paraaortic LND is left to the attending's discretion. We reviewed the surgeon's intraoperative findings based on the operative report and accounted for all metastatic nodes in the pathology report.

Results

Between 9/2005 and 4/2011, 498 patients with endometrial cancer underwent SLN mapping by 10 attending surgeons. All patients received an intracervical injection of blue dye. From the earlier time period of our SLN protocol, 34 patients also had a fundal injection of blue dye, and 75 had lymphoscintigraphy with Tc injection into the cervix as well.

Demographic and clinicopathologic characteristics of the study population are summarized in Table 1. The median age was 61 years (range, 33–88), with a median body mass index of 29.1 kg/m^2 (range, 15.7–68.7). One hundred eighty-nine cases (38%) were performed by laparoscopy, 189 (38%) by robotic-assisted laparoscopy, and 120 (24%) by laparotomy. Histology was distributed as follows: endometrioid, 393 (79%); serous, 44 (9%); clear cell, 10 (2%); carcinosarcoma, 27 (5%); and other, 24 (5%). The predominant FIGO stage was stage I (392 patients [79%]).

For the entire population of 498 patients in which SLN mapping was attempted (Table 2), the median SLN count was 3 (range, 0–15), and the median total LN count was 8 (range, 0–59). At least one SLN was detected in 401 cases (81%). There was unilateral pelvic