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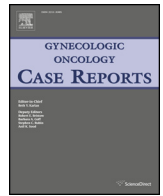
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## Case series

## Performance of sentinel lymph node biopsy in high-risk endometrial cancer



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## ABSTRACT

**Objective:** To determine the rate and performance of sentinel lymph node (SLN) mapping among women with high-risk endometrial cancers.

**Methods:** Patients diagnosed between 2012 and 2015 with uterine cancer of grade 3 endometrioid, clear cell, serous or carcinosarcoma histology and who underwent SLN mapping prior to full pelvic lymph node dissection were included. Subjects underwent methylene blue or ICG injection for laparoscopic (N = 16) or robotic-assisted laparoscopic (N = 20) staging. Outcomes included SLN mapping rates, SLN and non-SLN positive rates, false negative SLN algorithm rate, and the negative predictive value (NPV) of the SLN algorithm. Fisher's exact test was used to compare mapping and node positivity rates.

**Results:** 9/36 (25%) patients with high-risk uterine cancer had at least one metastatic lymph node identified. Successful mapping occurred in 30/36 (83%) patients. SLN mapped to pelvic nodes bilaterally in 20 (56%), unilaterally in 9 (25%), and aortic nodes only in 1 (3%). Malignancy was identified in 14/95 (15%) of all sentinel nodes and 12/775 (1.5%) of all non-sentinel nodes (p < 0.001). The false negative rate of SLN mapping alone was 2/26 (7.7%); the NPV was 92.3%. When the SLN algorithm was applied retrospectively the false negative rate was 0/31 (0%); the NPV was 100%.

**Conclusion:** SLN mapping rates for high-risk cancers are slightly lower than in prior reports of lower risk cancers. The NPV of the SLN mapping alone is 92% and rises to 100% when the SLN algorithm is applied. Such results are acceptable and consistent with larger subsets of lower risk endometrial cancers.

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## 1. Introduction

Endometrial cancer (EC) is typically treated surgically. Because of the adjuvant treatment implications, complete surgical staging including lymphadenectomy is recommended for high-risk ECs (Colombo et al., 2013). Sentinel lymph node (SLN) mapping has the potential to provide information about lymph node (LN) metastasis while avoiding potential complications of extended lymph node dissection (LND) (May et al., 2010).

Multicenter studies of detection rate, diagnostic accuracy, and impact of SLN biopsy in patients with low-risk EC suggest that SLN biopsy alone can accurately diagnose LN involvement (Raimond et al., 2014; Ballester et al., 2011). However, current data does not yet support substituting formal lymphadenectomy with SLN biopsy in high-risk EC

cases (Ballester et al., 2011; Naoura et al., 2015). The aim of this study is to determine the rate and performance of SLN mapping among women with high-risk ECs and to report the predictive value of the procedure and the corresponding algorithm.

## 2. Methods

We identified 36 patients with high-risk histology EC (carcinosarcoma, papillary serous, clear cell, or grade 3 endometrioid adenocarcinoma) who underwent SLN dissection followed by full pelvic LND at a single institution. Patients were retrospectively identified from 2 IRB-approved studies, neither of which mandated SLN biopsy. Hysterectomy type and decision to perform aortic lymphadenectomy were at the discretion of the surgeon.

The SLN procedure was performed by injecting 4 mL of either methylene blue or indocyanine green (ICG) dye into the cervix at 3 and 9 o'clock both superficially and deep during examination under anesthesia. Blue dye 1% (10 mg/mL) was used in all conventional laparoscopic

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cases; ICG dye was used in all robotic-assisted cases. Near infrared fluorescence imaging with the DaVinci robotic system was utilized to identify green SLNs.

The performance characteristics of SLN mapping alone were retrospectively evaluated and compared to characteristics yielded by applying the algorithm for SLN mapping of EC developed at Memorial Sloan-Kettering Cancer Center (MSKCC). The SLN algorithm requires (Colombo et al., 2013) peritoneal and serosal evaluation and washings; (May et al., 2010) retroperitoneal evaluation including excision of all mapped SLNs and removal of all suspicious nodes regardless of mapping; and (Raimond et al., 2014) if there is no mapping within a hemipelvis, a side-specific pelvic, common iliac, and interiliac LND should be performed. (Barlin et al., 2012)

Our institutional SLN sectioning protocol requires that each node have 7 levels cut, of which levels 1, 4, and 7 are stained with hematoxylin and eosin (H&E). If any of the H&E slides reveal suspicious, but non-diagnostic pathology, adjacent levels are stained for cytokeratin and reviewed for evidence of metastasis. A lymph node containing metastases of any size, including isolated tumor cells and micrometastases, is considered positive.

The central tendencies of BMI were compared using the Wilcoxon rank sum tests. Differences in proportions were compared using Fisher's exact test. The exact binomial method was used to calculate 95% confidence intervals for rates. Analyses were conducted using SAS v9.3 software (SAS Institute, Inc., Cary, NC). False negative rate was defined as the number of patients with negative SLNs but metastatic non-SLNs divided by all patients with negative SLN; this metric was calculated exclusively for pelvic node basins and not for metastases to the aortic region.

### 3. Results

Between August 2012 and June 2015, 36 patients with high-risk uterine cancers underwent SLN mapping prior to full pelvic LND. Median age was 66.6 years; median BMI was 32.3 kg/m<sup>2</sup> (Table 1). At least one SLN was identified in 30/36 (83%) patients: 20 (56%) had

**Table 1**  
Patient characteristics.

Parameter	Median	Range
Age (years)	66.6	27.5–81.5
BMI (kg/m <sup>2</sup> )	32.3	19.8–46.3
Parameter	N	%
Race/ethnicity		
Caucasian	24	67
African American	11	30
Other/not reported	1	3
FIGO stage		
I	1	3
IA	18	51
IB	6	16
II	1	3
IIIA	1	3
IIIC1	7	19
IIIC2	1	3
IVB	1	3
Histologic type		
Serous	8	22
Endometrioid	12	33
Clear cell	1	3
Carcinosarcoma	6	17
Adenocarcinoma, NOS	2	5
Mixed, including serous or clear cell	6	17
Undifferentiated	1	3
Surgical procedure		
Laparoscopy	16	45.3
Robotic assisted	20	55

**Table 2**  
Mapping rates.

Patient level mapping n = 36	Successful mapping	%
Bilateral mapping	20	56
Unilateral mapping	9	25
Para-aortic mapping	1	3
Surgical procedure		
Laparoscopic (n = 16)	12	75
Robotically assisted (n = 20)	18	90
		p = 0.37
Surgical procedure	Successful bilateral mapping	%
Laparoscopic (n = 16)	7	46
Robotically Assisted (n = 20)	13	65
		p = 0.32

bilateral pelvic SLN mapping, 9 (25%) unilateral pelvic SLN mapping, and 1 (3%) aortic SLN mapping. Rates of bilateral mapping by type of procedure were 7/16 (44%) for the laparoscopic approach and 13/20 (65%) for the robotic approach (p = 0.32; Table 2). Pelvic LNs were collected in 36/36 (100%) subjects and aortic nodes in 25/36 (69%) subjects.

From the 36 cases included in this cohort, 95 SLNs and 775 non-SLNs were removed. The median number of SLNs removed per case was 2 (range, 0–7) and the median number of non-SLNs (pelvic and aortic) removed per case was 22 (range, 4–40). Fourteen of 95 (15%) sentinel nodes and 12/775 (1.5%) non-sentinel nodes were malignant (p < 0.001, Table 3). Of the 14 SLNs containing metastatic disease, 2 (12%) were detected laparoscopically with methylene blue dye and 12 (86%), robot-assisted with ICG. Seven patients (19%) had 1 or more SLNs containing metastatic disease removed. 3/7 (43%) patients with metastatic SLNs also had positive non-sentinel nodes.

The 6 patients for whom no SLNs were identified went on to full lymphadenectomy; none of the additional nodes evaluated were malignant. Barriers to SLN identification included extensive adhesive disease, fibroids, or morbid obesity that impeded visualization and mobility. The median BMI of patients who mapped was 31.1 kg/m<sup>2</sup> compared to 34.9 kg/m<sup>2</sup> for patients who did not map (p = 0.2).

Nine of the 30 (30%) successfully mapped cases had metastatic disease to the SLNs, pelvic LNs, and/or aortic nodes. Metastases were limited to the SLNs in 4/9 cases, extended to both SLNs and non-sentinel nodes in 3/9 cases, and were observed only in non-sentinel nodes in 2/9 cases. These 2 cases were labeled as false-negatives, yielding a false-negative rate of 7.7% (95%CI, 0.1–25%).

Concerning the two false-negative cases: In the first case there was a suspicious, 3 × 3 cm firm LN located directly adjacent to 3 left pelvic SLNs. This instance of extra-uterine disease was captured by the SLN algorithm under the guidance that all grossly enlarged nodes are removed regardless of mapping. In the second case, several low right aortic SLNs were identified, but no right pelvic SLN was identified. Full pelvic LND was performed (as recommended by the algorithm due to non-mapping in the hemipelvis); the microscopically positive malignant non-SLN was removed from the right obturator space. Twelve additional non-SLNs from this patient were negative for metastatic disease.

Evaluation of the MSKCC SLN algorithm resulted in zero false-negative cases out of 32 cases with a negative algorithm result, yielding a false-negative rate of 0% (95%CI, 0–13%). The negative predictive value

**Table 3**  
Positivity rate by node type.

Type of node	Malignant status	%
Sentinel lymph nodes (n = 95)	14	15
Non-sentinel lymph nodes (n = 775)	12	1.5
		p < 0.001

of SLN algorithm in our high-risk cohort was therefore 100% (95%CI, 86.7–100%).

#### 4. Discussion

Systemic therapy is indicated for women with extra-pelvic disease, with therapeutic decisions directly influenced by the identification of nodal and distant metastasis. If lymph node status is unknown, there is a possibility that some patients may be over- or undertreated (Leitao & Barakat, 2011).

In this single institution analysis of SLN mapping among subjects with histologic high-risk features, we report an NPV of 92% for mapping alone and 100% using the MSKCC algorithm. Prior literature on SLN mapping includes analyses of patient cohorts who underwent mapping without consideration to grade and histology (May et al., 2010; Raimond et al., 2014; Brucker et al., 2014). Our NPV rate is comparable to rates previously reported for early stage EC (Ballester et al., 2011). Our data suggest that the implementation of an EC surgical algorithm with SLN mapping and biopsy may be a successful method of identifying metastatic nodal disease in the majority of patients with high-risk uterine cancers.

The overall rate of successful SLN mapping in this cohort was 83%, while the bilateral mapping rate was 56%. The overall mapping rate reported in the literature ranges widely from 45 to 100%, with techniques differing in injection site and depth as well as mapping medium and volume injected (Ballester et al., 2011; Abu-Rustum et al., 2009; Jewell et al., 2014; Frumovitz et al., 2007). Our detection rate is comparable to cohorts that underwent similar mapping protocols (Naoura et al., 2015; Jewell et al., 2014; Frumovitz et al., 2007). Overall mapping rates have significantly improved by using ICG instead of blue dye (Jewell et al., 2014; Plante et al., 2015). Our findings are consistent with this observation; the mapping rate of metastatic SLNs was 90% in the current study when using ICG compared to 75% using blue dye ( $p = 0.05$ ).

In the current series, the extent of paraaortic LND was at the discretion of the attending surgeon and was variable. Capturing instances of isolated paraaortic disease is a limitation to the exclusive use of SLN mapping in women with high-risk uterine cancers (Barlin et al., 2012; Boronow, 2008; Frumovitz et al., 2014). The false negative rate of sentinel aortic nodes to the para-aortic LNs could not be reported here due to the low incidence of successful sentinel aortic node mapping. However, our group is moving toward more robust paraaortic node dissection following identification of pelvic SLN alone in patients with high-risk histologies.

It has been observed in several malignancies that in the presence of gross metastasis, mapping dyes may approach a diseased node without illuminating it (Tanner et al., 2015). This represents a fundamental limitation to SLN mapping alone for the identification of extra uterine disease in cases of high-risk histology. Applying the SLN mapping algorithm increases the likelihood of identifying metastatic disease in these patients.

While the relatively small size of this cohort represents a major limitation to this study, the number of high-risk cases described here is comparable to the volumes reported in other single-institution reviews (Naoura et al., 2015). Similarly, the analyses conducted here were restricted to cases wherein SLN mapping was successful and complete lymphadenectomy was done, excluding cases where SLN mapping

was performed but no further LND was conducted may represent selection bias. Other limitations include the use of two different surgical approaches and dye agents. However we feel that analysis of available data on SLN in this high-risk cohort will contribute to refinement of the predictive algorithm and further support its application during lymph node dissection. Ultimately, our results support the use of SLN procedure for women with high-risk histology EC.

#### Conflict of interest

Dr. Alvarez Secord reports grants from Tesaro, Astra Zeneca, Eisai Morphotek, Bristol Myers Squibb, Incyte, Astellas Pharma Inc., Amgen, Endocyte, Boehringer Ingelheim, Astex Pharmaceuticals Inc., and grants and/or personal fees from Genentech, Exelixis, Janssen, and Precision Therapeutics outside the submitted work. Ms. Broadwater reports grants from NIH during the conduct of the study. No other authors have conflicts to disclose.

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