
# Mapping the landscape of sentinel lymph nodes in endometrial cancer: let us continue in the right direction

Ryan Kahn , Mario Leitao

Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA

**Correspondence to**
Dr Mario Leitao, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA; leitaom@mskcc.org

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Over a decade ago, two randomized controlled trials demonstrated that pelvic lymphadenectomy added to standard hysterectomy with bilateral salpingo-oophorectomy for the treatment of newly diagnosed endometrial cancer did not confer a therapeutic benefit.[1 2] These trials have been heavily criticized by lymphadenectomy proponents. Of note, routine lymphadenectomy to the renal veins was never established as 'standard' care by any level 1 evidence. There is no therapeutic value to removing normal-appearing lymph nodes. However, surgical nodal assessment provides enhanced staging and helps guide post-operative treatment strategy.

Comprehensive lymphadenectomy is associated with significant short- and long-term morbidity. Sentinel lymph node (SLN) mapping, which has already been established in other cancers, represents a happy medium. SLN mapping in endometrial cancer has been increasingly assessed and used, demonstrating safety, feasibility, and high sensitivity with a low-false positive rate, as well as a significantly decreased risk of lymphedema compared with lymphadenectomy.[3–6] Furthermore, ultrastaging of SLNs allows for the identification of low-volume metastasis that may be missed by conventional methods. SLN assessment is now widely accepted as an effective means for guiding post-operative management of endometrial cancer, helping preclude under- or over-treatment, compared with performing a hysterectomy and using uterine features.[7] It is important that we optimize SLN mapping detection since we now rely heavily on the identification of only a few nodes.

Raffone et al report the results of their systematic review and meta-analysis assessing predictive factors of failed SLN mapping, defined as an inability to identify at least one SLN in each hemi-pelvis, in patients with endometrial cancer.[8] Their analysis included observational cohort studies that assessed predictive factors of failed SLN mapping in patients with early-stage endometrial cancer undergoing SLN biopsy using an indocyanine green (ICG) cervical injection. They identified six studies, published between 2016 and 2020, with a total of 1345 patients for final analysis. Factors shown to have a significant association with failed SLN mapping included advanced-stage disease, an ICG dose <3 mL, enlarged lymph nodes, and lymph node involvement with disease. Other factors, such as body mass index (BMI) >30 kg/m$^2$, menopausal status, adenomyosis, prior pelvic surgery, lysis of adhesions, deep myometrial invasion, grade 3 disease, histotype, and lymphovascular space invasion, were not significantly associated with failed SLN mapping. This information provides important information as we continue to work towards improving SLN mapping techniques.

We commend the authors for this undertaking. With rates of failed SLN mapping for endometrial cancer as high as 20–25% worldwide, more efforts like these are needed to help us continue to improve on this practice.[9] However, the study also has some limitations and may not apply to all surgeons who perform SLN mapping. The studies for analysis included by Raffone et al did not report whether there was nodal tissue in the final pathology. Therefore, cases with a lack of lymphatic tissue in the specimen were not reported, which could have falsely increased the rate of successful mapping. Furthermore, the experience and learning curve of each surgeon is an important variable in any surgical study, which is one of the most important confounding factors and is nearly impossible to control for in adjusted analyses. Therefore, the generalizability of the results needs to be considered. Enlarged lymph nodes on pre-operative imaging were used as a predictive variable. However, the definition of an 'enlarged' lymph node was not clearly defined across the studies. A defined size threshold for successful mapping may have significant value when planning surgeries. We found it interesting that a 30 kg/m$^2$ BMI cut-off was used. This may explain why BMI was not associated with failed SLN mapping. Data from our institution noted a significantly lower bilateral SLN mapping rate in patients with a BMI >40 kg/m$^2$ using ICG.[10]

The factors found to be significantly associated with failed SLN mapping in the current study were advanced stage, enlarged nodes, and nodal metastases. These are already considered possible factors affecting SLN mapping success, which this

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study confirms. One theory to explain why these factors impede successful mapping is that tumor emboli within the lymphatic channels and nodes impair the ability of dye flow. Of note, all of these factors are highly correlated and unlikely to be independent factors, meaning an enlarged node is likely to harbor cancer, which would upstage disease. In sum, this study further confirms the need to follow an SLN mapping algorithm, such as the one published by Memorial Sloan Kettering Cancer Center, for successful mapping.

As SLN assessment in endometrial cancer continues to become more widely used, addressing the technique and success of mapping is only one of the many pieces of the puzzle. As with any evolving and novel technique, more questions arise than are answered. It is evident that patients with macrometastasis benefit from post-operative chemotherapy[11]; however, the management of patients with low-volume metastasis, especially isolated tumor cells (ITCs), identified in 3–10% of patients, remains unclear and heavily debated.[11 12] A recent survey by the Society of Gynecologic Oncology demonstrated that 70% of respondents are now practicing SLN mapping; however, there are no clear management guidelines when ITCs are identified.[13] A major reason is the lack of standardization in the histopathologic diagnosis. ITCs are defined as a cluster of cells no larger than 0.2 mm; single tumor cells; or a cluster of <200 cells in a single cross-section. What if there is a discrepancy between size and cell count? Should count trump size or vice versa? Are abutting cells or clusters considered the same as distant clusters? These are questions that need to be considered as we move towards a more standardized classification system, which is necessary for accurate reporting and the design of future studies. Until we learn more from prospective studies, ITC status should not yet undergo automatic placement into categories of positive or negative. Instead, it should be looked at as an integral part of a larger picture, combined with other factors, including but not limited to lymphovascular invasion, grade, tumor size, washings, age, and comorbidities, to optimize the management of the individual patient.

SLN mapping for endometrial cancer is also confronted with the increasing use of pathologic/molecular characterization. This is of exceeding relevance as the technology to classify tumors into the four subtypes set by The Cancer Genome Atlas (TCGA) project are becoming more affordable and accessible.[14] Although this is a bright age for molecular medicine, we cannot just move past SLN mapping. It would be a disservice to throw away years of work with SLN assessment, which has shown a clear benefit in the staging and treatment for our patients. Molecular characterization should serve as an incorporation and not a replacement. We must work towards integrating SLN status and molecular subtype to complement each other, as this will give us a better understanding of an individual patient's tumor.

The article by Raffone et al[8] will certainly add to the current literature surrounding the art of SLN mapping. The results of this study provide us with useful information to work towards the overarching goal of successful SLN assessment—detecting low-volume endometrial cancer while decreasing the risk of comorbidities for our patients. As we improve SLN identification, we must also build on the classification of pathologic and molecular findings to elevate this modality to its full potential.

**Twitter** Mario Leitao @leitaomd

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**ORCID iDs**
Ryan Kahn http://orcid.org/0000-0002-5596-6238
Mario Leitao http://orcid.org/0000-0003-0818-3836

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