Research Report

Clinical factors associated with failed sentinel lymph node mapping in endometrial cancer

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**ABSTRACT**

Objective: Sentinel lymph node (SLN) mapping is a highly accurate surgical technique for detecting metastases in endometrial cancer. The objective of this study was to identify critical clinical factors associated with failed mapping.

Methods: All patients with endometrial cancer undergoing minimally-invasive staging and planned SLN biopsy from 1/1/2017 to 12/31/2020 at a single institution were identified retrospectively. Demographic, clinicopathologic and treatment data were obtained. Data were compared using descriptive statistics. Univariate and multivariable logistic regression were performed to identify predictors of failed mapping.

Results: 819 patients were identified with a mean age of 64.6 years (range 26–93) and mean BMI of 35.6 kg/m² (range 18–68). Most (88.5 %, 725/819) had early-stage disease and endometrioid histology (82.3 %, 674/819). A majority (74.2 %, 608/819) had successful bilateral mapping, and 54 (6.6 %) had unsuccessful bilateral mapping. Increasing BMI was significantly associated with unsuccessful bilateral mapping: patients with BMI > 30 were more likely to have unsuccessful SLN mapping (p = 0.033). Among patients with known lymph node status (799/819), patients with macrometastases and micrometastases were more likely to have failing bilateral mapping compared to those with negative SNs or isolated tumor cells (p = 0.013). On multivariable analysis, higher BMI and histology were associated with failing bilateral mapping (OR = 1.023, 95 % CI (1.005, 1.041) and OR = 1.678, 95 % CI (1.177, 2.394), respectively).

Conclusion: SLN mapping has a high success in patients undergoing minimally-invasive surgical staging for endometrial cancer. Increasing BMI, high risk histology, and lymph node metastases are risk factors for failed mapping.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 66,570 new cases and 12,940 deaths in 2021. (Figures, 2021) Traditionally, treatment of early stage endometrial cancer has consisted of hysterectomy, salpingo-oophorectomy, and selective pelvic and para-aortic lymphadenectomy. Given the potential morbidity associated with full lymphadenectomy and overall low incidence of lymph node metastases in low risk endometrial cancer patients, selective lymphadenectomy based on the Mayo Criteria offered an alternative to pelvic and para-aortic lymphadenectomy for patients with low risk disease. (Mariani et al., 2000) More recently, sentinel lymph node (SLN) mapping has emerged as a surgical technique with a high degree of accuracy in detecting metastases and low morbidity, making it a preferred alternative to selective lymphadenectomy. (Rossi et al., 2017) This technique has been increasingly adopted in all grades of endometrial cancer staging. (Soliman et al., 2017).

According to current National Comprehensive Cancer Network (NCCN) guidelines, failure of SLN mapping requires the performance of side-specific full lymphadenectomy or utilization of tumor factors provided on frozen pathologic assessment at the time of surgery to determine if a full lymphadenectomy is indicated. (NCCN Version 1.2022) Full lymphadenectomy is associated with increased morbidity, including lymphocele formation and chronic lymphedema in up to 50 % of patients. (Pigott et al., 2020; Yost et al., 2014) Retrospective data from small series suggests that risk factors for SLN mapping failure include clinically enlarged or positive lymph nodes, obesity, and use of various
dye techniques. (Tortorella et al., 2019; Eitan et al., 2015; Sozzi et al., 2020; Rozenholc et al., 2019; Holloway et al., 2017) Clinical predictors of failed mapping would allow for identification of patients at higher risk for requiring full lymphadenectomy and therefore would be valuable for accurate preoperative counseling. The objective of this study was to identify clinical factors associated with failed SLN mapping in a large cohort of patients with clinical stage I endometrial cancer undergoing minimally-invasive surgical staging and planned SLN biopsy with intracervical injection.

2. Methods

The University of Pittsburgh Institutional Review Board approved this retrospective cohort study. All patients with clinical stage I endometrial cancer undergoing minimally-invasive surgical staging and planned SLN biopsy from 1/1/2017 to 12/31/2020 at three locations within a single academic institution were identified retrospectively. All patients underwent minimally-invasive total hysterectomy, bilateral salpingo-oophorectomy and intracervical injection of dye for SLN mapping. Patients were excluded if they had a history of prior retroperitoneal surgery. Patients were also excluded if SLN dissection was not performed due to patient factors including difficult ventilation, intolerance of steep Trendelenburg positioning, unanticipated intraperitoneal dye techniques requiring extensive lysis of adhesions for over 60 min, as well as clinically enlarged and/or concerning lymph nodes intraoperatively.

Successful SLN mapping was defined as identification of bilateral SLNs, whereas failed SLN mapping was defined as unilateral or no SLN mapping. In cases of failed mapping, the surgeons in this cohort either 1) performed side-specific full lymphadenectomy regardless of intraoperative tumor features or 2) used Mayo Clinic criteria and performed side-specific lymphadenectomy only for high-risk tumors.

Demographic, clinicopathologic and treatment data were collected through electronic medical record review. Patient data included age, race, body mass index (BMI), number of comorbidities, tobacco use, and history of prior cervical procedures (loop electrosurgical excision procedure or cold knife conization). Surgical data included type of procedure (laparoscopic or robotic-assisted) and type of intraoperative dye. Pathologic data included stage, histology, presence of lymphovascular space invasion (LVSI), depth of invasion, cytology status, and nodal status.

Statistical analyses were conducted using Stata (StataCorp LLC, College Station, TX). Descriptive statistics were reported for baseline demographic, pathologic, operative and treatment variables. Categorical variables were compared using Chi Square and continuous variables were analyzed using two-tailed t-tests. Univariate and multivariable logistic regression were performed to identify predictors of failed mapping. All analyses were conducted using Stata (StataCorp LLC, College Station, TX). A p-value < 0.05 was considered statistically significant.

3. Results

During the study period, 819 patients met inclusion criteria (Fig. 1). The mean age was 64.6 years (range 26–93), the mean BMI was 35.6 kg/m² (range 18–68), and mean number of comorbidities was 3.7 (range 0–22) (Table 1). The majority of patients (76.4 %, 626/819) had laparoscopic surgery, while 23.6 %% (193/819) had robotic-assisted surgery. On final pathology, most patients (88.5 %, 725/819) had early-stage disease, while 11.5 % (94/819) had stage III or IV disease. Five patients had stage IV disease noted on final pathologic review, four of which had microscopic omental metastases and one with metastatic disease on a sigmoid epiploic nodule. Endometrioid histology was most common (82.3 %, 674/819). Intracervical isocyanine green (ICG) injection was used for 98.8 % of patients (809/819) and methylene or isosulfan blue was used for 1.2 % (10/819). There were nine attending surgeons represented in this cohort who performed a median of 84 cases per surgeon during the study period (mean 91 cases per surgeon, range 55–127).

The overall detection rate, defined as SLN mapping of at least one SLN, was 93.4 % (765/819). Most patients (74.2 %, 608/819) had successful bilateral SLN mapping and 157 (19.2 %) had unilateral SLN mapping. A minority of patients (6.6 %, 54/819) had unsuccessful bilateral SLN mapping. Of the 54 patients with unsuccessful bilateral mapping, 31 had further lymph node assessment with full bilateral pelvic lymphadenectomy with an average of 9 total lymph nodes removed (range 2–23). Two of these patients (6.5 %) underwent selective paraaortic lymphadenectomy per the primary surgeon’s discretion with an average of 6 lymph nodes removed (range 4–8).

Successful SLN mapping was defined as identification of bilateral SLNs, whereas failed SLN mapping was defined as unilateral or no SLN mapping. For patients with known lymph node status who had at least one lymph node obtained (799/819), 9 % had nodal involvement; 4 patients (0.5 %) patients had nodal micrometastasis, 35 (4.4 %) had nodal macrometastasis, and 33 (4.1 %) had isolated tumor cells (ITCs).

![Fig. 1. Patient selection criteria MIS = minimally-invasive surgery; SLN = Sentinel lymph node; LOA = lysis of adhesions.](image-url)
Table 1
Univariate analysis of predictors of failed bilateral sentinel lymph node mapping.

| Clinical Variable          | Total n (%) | Successful Bilateral SLN Mapping n = 608 | Failed Bilateral SLN Mapping n = 211 | P value |
|----------------------------|-------------|-----------------------------------------|--------------------------------------|---------|
| Age at Diagnosis, mean (range) | 64.6 (26–93) | 64.3 (26–90) | 65.5 (30–93) | 0.108 |
| BMI at Diagnosis, mean (range) | 35.6 (18–68) | 35.2 (18–68) | 36.8 (20–64) | 0.002 |
| Number                      | 3.7 (0–22)   | 2.5 (0–22)  | 3.7 (0–14)    | 0.632 |
| Comorbidities, mean (range) | 0.6 (0.3)    | (0.3)       | (0.5)        |       |
| Racea                       | 766 (571)    | 519 (195)   | 150 (30.9)    | 0.309 |
| White                       | (95.6) (95.8) | (95.1) (9)  | (95.1) (9)    |       |
| Black                       | (3.2) (4)    | (4.4) (1)   | (4.4) (1)     |       |
| Asian                       | (3.5) (7)    | (0.7) (2)   | (0.5) (0)     |       |
| Other/multiple              | (0.6) (2)    | (0.3)       | (0.3)        |       |
| Tobacco Use                 | 584 (434)    | 345 (150)   | 150 (30.9)    |       |
| Never                      | (71.3) (71.4) | (71.1) (48) | (71.1) (48)   |       |
| Former                     | 167 (93.5)   | (22.8) (13) | (22.8) (13)   |       |
| Current                     | 68 (20.4)    | (6.2)       | (6.2)        |       |
| History of Cervical Procedure | 781 (580)   | 201 (101)   | 100 (50)      | 0.936 |
| No                         | 38 (4.6)     | 13 (3.2)    | 13 (3.2)      |       |
| Yes                        | 507 (369)    | 138 (69)    | 69 (34.6)     | 0.225 |
| Surgeon by Volumeb         | (61.9) (60.7) | (55.4) (73) | (55.4) (73)   |       |
| High                       | 312 (39.3)   | (34.6)      | (34.6)       |       |
| Low                        | (38.1)       | (34.6)      | (34.6)       |       |
| Type of Surgery            | 626 (468)    | 158 (74.9)  | 74.9 (53)     | 0.537 |
| Laparoscopic               | (76.4) (77.4) | (74.9) (53) | (74.9) (53)   |       |
| Robotic-assisted           | (23) (25.1)  | (25.1)      | (25.1)       |       |
| Type of Dye                | 809 (601)    | 208 (98.6)  | 98.6 (3)      | 0.723 |
| ICG                        | (98.8) (98.9) | (98.6) (3) | (98.6) (3)    |       |
| Methylen blue              | 10 (1.2)     | (1.4)       | (1.4)        |       |
| Stage Early                | 725 (536)    | 189 (105)   | 105 (57.8)    | 0.578 |
| (I and II) Advanced (II and IVB) | 617 (472) | 145 (69.1) | 69.1 (35)   | 0.010 |
| Histology                  | (75.6) (77.9) | 134 (69.1) | 69.1 (35)   |       |
| Endometrioid               | 59 (22.1)    | (31)        | (31)         |       |
| Non-endometrioid           | (24.4)       | (31)        | (31)         |       |
| LVSI                       | 504 (379)    | 125 (59.2)  | 59.2 (26)     | 0.426 |
| Absent                     | (61.5) (62.3) | (59.2) (26) | (59.2) (26) |       |
| Present                    | 315 (37.7)   | (40.8)      | (40.8)       |       |
| DOI                        | 555 (405)    | 150 (71.1)  | 71.1 (31)     | 0.230 |
| < 50 %                     | (67.8) (66.6) | (71.1) (31) | (71.1) (31) |       |
| ≥ 50 %                     | 264 (334)    | (28.9)      | (28.9)       |       |
| Cytology                   | 647 (408)    | 167 (79.2)  | 79.2 (24)     | 0.670 |
| Negative                   | (79.8) (79.6) | (79.2) (24) | (79.2) (24) |       |
| Positive                   | (10.4) (10.4) | (11.4) (10) | (11.4) (10) |       |
| Suspicious/Atypical        | 46 (5.9)     | (4.7)       | (4.7)        |       |
| Not Obtained               | (5.6) (5.1)  | (4.7)       | (4.7)        |       |
| Nodal Status               | 707 (536)    | 171 (71)    | 71 (34)      | 0.013d |
| Negative                   | (88.5) (88.2) | (89.5) (4) | (89.5) (4) |       |
| ITC                        | 33 (4.8)     | (2.1)       | (2.1)        |       |
| Micrometastases            | (4.1) (4.1)  | (1.4)       | (1.4)        |       |
| Macrometastases            | (0.5) (0.5)  | (0.3)       | (0.3)        |       |

Sum of percentages may not equal 100% due to rounding.

Abbreviations: SLN = sentinel lymph node; BMI = body mass index; LVSI = lymphovascular space invasion; DOI = depth of invasion; ITC = isolated tumor cell.

*a18 patients with missing data.
*bTotal number of cases performed during study time period.
*d20 patients excluded from analysis for unknown nodal status.

When comparing by mapping status, patients with macrometastases and micrometastases were more likely to have failed bilateral mapping compared to those with negative nodal status or ITCs (p = 0.013).

On univariate analysis (Table 1), BMI at diagnosis and histology were significantly different between successful and failed mapping groups (p = 0.032 and p = 0.01, respectively). When tumors with grade 1 and 2 endometrioid histology were compared to tumors with grade 3 endometrioid and non-endometrioid histology, there was no significant difference in SLN mapping success. Of the 145 patients with non-endometrioid histologies in this cohort, 42 (29 %) were serous, 13 (9 %) were clear cell, 28 (19.3 %) were carcinosarcoma, 55 (37.9 %) were mixed endometrioid and other high grade histology, and 7 (4.8 %) were other histologies. Tobacco use, history of prior cervical procedures, surgeon volume and other pathologic factors were not associated with failed mapping. On multivariable analysis, higher BMI and non-endometrioid histology remained significantly associated with failed mapping. Lymph node status was not able to assessed on multivariable analysis due to the small number of patients who had unknown lymph node status.

Increasing risk of failed bilateral SLN mapping was seen in higher BMI categories using different BMI cutoffs. Specifically, patients with a BMI > 30 were significantly more likely to have unsuccessful SLN mapping compared to patients with a BMI < 30 (OR = 1.519, 95 % CI (1.033, 2.233), p = 0.033, Fig. 2).

4. Discussion

This study demonstrates a high success rate of SLN mapping in a large cohort of patients with clinical stage I endometrial cancer undergoing minimally-invasive surgical staging. Increasing BMI, non-endometrioid histology, and lymph node macrometastases were identified as risk factors for unsuccessful bilateral SLN mapping.

Large clinical trials have demonstrated the feasibility and high success rates of SLN mapping for patients with clinically early stage endometrial cancer. Numerous studies have determined that the intracervical SLN mapping technique has both a high sensitivity and negative predictive value for the detection of lymph node metastases. (Rossi et al., 2017; Ballester et al., 2011) Additionally, this technique is associated with significantly decreased surgical morbidity from chronic lymphoedema. (Glaser et al., 2021) As a result, SLN mapping has emerged as a viable strategy to replace traditional full lymphadenectomy, and the NCCN guidelines now support the use of SLN mapping as an alternative to full lymphadenectomy for the surgical staging of apparent early stage disease. (xxxx) The SLN algorithm requires removal of any suspicious or grossly enlarged nodes regardless of mapping status as well as site-specific full nodal dissection in the event of failed SLN mapping. Alternatively, utilization of intraoperative tumor factors may also be used to

Fig. 2. Percentage of Failed SLN Mapping by BMI Category.
determine the need for full lymphadenectomy. (xxxx).

Initial SLN mapping trials demonstrated high rates (86–89 %) of successful SLN mapping of at least one lymph node; however, successful bilateral SLN mapping rates were lower at approximately 52–62 %. (Rossi et al., 2017; Ballester et al., 2011) Numerous studies have demonstrated that utilization of ICG dye results in superior successful SLN mapping rates when compared to blue dye alone. (Holloway et al., 2017) More recent retrospective studies demonstrated increasing successful bilateral SLN mapping rates of approximately 74–78 % when ICG dye is used. (Tortorella et al., 2019; Sozzi et al., 2020; Taşkıncı et al., 2019) These series evaluated risk factors for failed bilateral SLN mapping; however, they included small numbers of patients and report conflicting results. One study of 327 patients demonstrated a successful bilateral mapping rate of 78.3 % and on multivariable analysis found lysis of adhesions at the beginning of the procedure and visibly enlarged lymph nodes to be independently predictive of failed mapping. In this study, the procedure success rates improved from 57.7 % to 83.3 % over the two year study period. (Tortorella et al., 2019) A separate study of 101 patients demonstrated a similar successful bilateral mapping rate of 74.3 %. However, the authors found no significant risk factors for failed bilateral SLN mapping, including BMI, surgeon experience with procedure, cervical and uterine lengths, amount of ICG dye injected, and other tumor factors. (Taşkıncı et al., 2019) A third study described 376 patients undergoing SLN mapping and reported a bilateral successful SLN mapping rate of 76.3 %. On multivariable analysis, LVSI, non-endometrioid histology, and intraoperative findings of enlarged lymph nodes were identified as predictors of failed bilateral SLN mapping. (Sozzi et al., 2020).

Our study demonstrated a bilateral SLN mapping success rate of 74.2 %, which is consistent with the aforementioned studies where ICG dye was used. However, in contrast to these studies, we found that increasing BMI was a significant clinical risk factor for unsuccessful bilateral SLN mapping. Notably, a very recent study of 764 patients from four Italian cancer centers also supports these findings. The authors of this study divided their study population by BMI < and ≥ 30 kg/m² and found that, after propensity-matching for age, presence of LVSI and histology, BMI was a significant predictor of unsuccessful bilateral SLN mapping, with a 1.156-fold increase in the risk of mapping failure for every-five units of BMI increase. (Vargiu et al., 2022).

Our study found no significant difference in mapping rates with surgeon volume. We defined high volume as > 100 cases in the study time frame and low volume as < 100 cases in the study time frame. Our institution began to universally perform SLN mapping and biopsy in 2017, at which time this technique was novel to all of our surgeons. We did not examine the SLN mapping success rate over time and therefore cannot make any conclusions regarding provider experience and SLN mapping success. Additionally, the intracervical ICG dye injections were performed either by the attending physician or resident/fellow trainee as per the attending discretion and was not an identifiable variable for this study.

Given that not every patient in our study who had failed SLN mapping underwent subsequent full lymphadenectomy due to surgeon discretion in the event of otherwise low risk primary tumor features, the lymph node status for a minority of patients was unknown. Therefore, lymph node pathologic status was unable to be included in the multivariable analysis. However, on univariate analysis, our study found that among patients with known lymph node status, patients with SLN macrometastases who were more likely to have failed mapping compared to those with negative status or isolated tumor cells on SLN biopsy. Our findings that lymph node metastases are associated with failed bilateral SLN mapping add to existing evidence that pathologically involved lymph nodes may interrupt normal lymphatic channel drainage and lead to failed SLN mapping. (Goyal et al., 2005) This supports the clinical rationale to proceed with side-specific full lymphadenectomy in patients with risk factors identified on intraoperative pathologic assessment and provides a compelling argument against changing this surgical approach by using intraoperative tumor features, as this may increase the risk of missing lymph node metastases.

To our knowledge, our study represents the largest reported cohort of patients undergoing minimally-invasive surgical staging with intracervical ICG injection for SLN mapping in clinical early stage endometrial cancer. A major strength of this study is the large number of patients included as well as the large number of surgeons performing the procedures. This study provides further evidence that SLN mapping is a feasible and successful technique in the surgical staging of endometrial cancer. Additionally, this study includes a significant number of patients with high risk histologies. Limitations of this study include its retrospective nature as well as lack of long-term outcome data.

Increasing BMI as a risk factor for unsuccessful bilateral SLN mapping is an important finding as this information will better inform preoperative patient counseling on the risk of failed SLN mapping and the potential need for full lymphadenectomy which is associated with increased surgical morbidity. Particularly for obese individuals who carry a higher baseline risk of developing lymphedema, this information will enable patients to have a more accurate understanding of the likelihood for full lymphadenectomy as well as the chronic complications such as lymphocele and/or lymphedema which could result from these procedures.

Importantly, we excluded patients from this study that had clinically enlarged or suspicious nodes at the time of surgery, given that removal of these nodes is recommended regardless of mapping status. Additionally, identification of macrometastases as a predictor of unsuccessful bilateral SLN mapping raises several important questions, including if failed SLN mapping indicates an increased risk of lymph node metastases and should a side-specific full lymphadenectomy be performed in all cases of failed SLN mapping, even for otherwise low risk primary tumors.

We excluded patients who had extensive lysis of adhesions: >60 min at the beginning of the case. A prior study reports that lysis of adhesions at the beginning of a surgery is a risk factor for failed mapping. (Tortorella et al., 2019) However, we propose that the inability to detect SLN mapping after extensive lysis of adhesions results from improper timing of SLN injection and is not necessarily a reflection of successful or unsuccessful mapping itself. For patients with complex surgical histories, we recommend consideration of intracervical ICG dye injection after access to the peritoneal cavity has been obtained and an intraabdominal survey to assess for adhesive disease has been performed.

In conclusion, this study demonstrates that SLN mapping has a high success rate within a large cohort of clinically early-stage patients undergoing planned minimally-invasive surgical staging for endometrial cancer. Increasing BMI, non-endometrioid histology, and lymph node macrometastases were identified as risk factors for unsuccessful bilateral SLN mapping.

CRediT authorship contribution statement

Alison A. Garrett: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. Alyssa Wield: Data curation, Writing – review & editing. Brigid Mumford: Data curation, Writing – review & editing. Isabel Janmey: Data curation, Writing – review & editing. Li Wang: Formal analysis, Writing – review & editing. Philip Grosse: Formal analysis, Writing – review & editing. Emily MacArthur: Data curation, Writing – review & editing. Ronald Buckanovich: Writing – review & editing. Madeleine Courtney-Brooks: Writing – review & editing. Paniti Sukumvich: Writing – review & editing. Jessica Berger: Writing – review & editing. Alexander B. Olawaiye: Writing – review & editing. Haider Mahdi: Writing – review & editing. Michelle Boisen: Writing – review & editing. Robert P. Edwards: Writing – review & editing. LaCoffman: Writing – review & editing. Sarah E. Taylor: Formal analysis, Methodology, Writing – review & editing. Jamie Lesnock: Conceptualization, Methodology, Supervision, Writing – review & editing.
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