Gynecologic Oncology 154 (2019) 34–38

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Sentinel lymph node biopsy with cervical injection of indocyanine green in apparent early-stage endometrial cancer: predictors of unsuccessful mapping

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HIGHLIGHTS

- The rate of failed unilateral or bilateral sentinel lymph node mapping is 21.7%.
- The presence of enlarged lymph nodes and lysis of adhesions are independently associated with an unsuccessful procedure.
- The expertise of the surgeon is associated with a successful procedure and consequent decreases in operative time

ARTICLE INFO

Article history:
Received 20 May 2019
Received in revised form 31 July 2019
Accepted 4 August 2019
Available online 8 August 2019

Keywords:
Endometrial cancer
Indocyanine green
Lymph nodes
Sentinel lymph node mapping
Stage I

ABSTRACT

Objective. To identify predictors of unsuccessful sentinel lymph node (SLN) mapping in patients with apparent early-stage endometrial cancer (EC) undergoing surgical staging with cervical injection of indocyanine green and SLN biopsy.

Methods. We retrospectively identified consecutive patients with EC with attempted SLN biopsy between June 2014 and June 2016 at our institution. Patients were grouped according to whether they had a *successful procedure*, defined as the bilateral identification of SLNs, or an *unsuccessful procedure*, defined as unilateral or no SLN mapping. Logistic regression was used to evaluate predictors of an unsuccessful procedure.

Results. Among 327 patients included in the analysis, 256 (78.3%) had a successful procedure and 71 (21.7%) had an unsuccessful procedure (15.0% unilateral SLN mapping, 6.7% no mapping). The rate of successful procedure increased from 57.7% to 83.3% between the first and last quarters of the 2-year study period, which represented the learning curve for the technique. The mean (SD) operative time decreased from 164 (55) to 137 (37) minutes. By multivariable analysis, lysis of adhesions at the beginning of surgery (odds ratio, 3.07; 95% CI, 1.56–6.07) and the presence of enlarged lymph nodes (odds ratio, 4.69; 95% CI, 1.82–12.11) were independently associated with an unsuccessful procedure.

Conclusions. Lysis of adhesions at the beginning of surgery and the presence of enlarged lymph nodes independently affect the bilateral detection of SLNs.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in the United States, with 63,230 estimated new cases in 2018 [1]. Total hysterectomy with bilateral salpingo-oophorectomy and lymph node assessment (pelvic and/or paraaortic lymphadenectomy) represent the traditional surgical approach for staging of apparent early-stage EC

Abbreviations: BMI, body mass index; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; ICG, indocyanine green; LVSI, lymphovascular space invasion; OR, odds ratio; SLN, sentinel lymph node.

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https://doi.org/10.1016/j.ygyno.2019.08.008
0090-8258/

[2]. The prognostic value of nodal status is clear because the stage of EC significantly affects survival and recommended adjuvant treatment. However, because the percentage of patients with positive lymph nodes is relatively low (10%), performing pelvic and/or paraaortic lymphadenectomy in every case potentially puts many patients at unnecessary risk for both procedure-related complications such as lymphedema and decreased quality of life [3].

For this reason, the concept of sentinel lymph node (SLN) biopsy was introduced, with the aim of decreasing the morbidity associated with lymphadenectomy without negatively affecting surgical staging and outcomes. The SLN technique is based on identifying major lymphatic pathways that drain the uterus and excising the primary identified node.

Prospective data have demonstrated that SLN biopsy accurately identifies positive lymph nodes with high sensitivity and high negative predictive value [4,5]. Furthermore, similar oncologic outcomes have been reported in retrospective comparative analyses between cohorts of patients undergoing full lymphadenectomy versus SLN biopsy in cases with low-risk pathologic features [6] and also with higher-risk histologic findings [7,8].

Despite these encouraging results, the use of the SLN technique to detect lymph node metastasis is still debated. According to National Comprehensive Cancer Network guidelines, SLN mapping may be considered in early-stage EC; they advocate strict adherence to the algorithm, with side-specific lymphadenectomy in patients who have unsuccessful mapping and with removal of all enlarged lymph nodes [9]. This allows for assessment of lymph node status and minimizes the risk of undertreatment.

In this context, achieving the highest rate of SLN mapping translates into fewer side-specific lymphadenectomies performed. Identifying predictors of unsuccessful procedures could be important for decreasing surgical morbidity and postoperative complications. Prior studies have demonstrated an association between failure of SLN mapping and increased body mass index (BMI) and/or clinically enlarged lymph nodes. However, these analyses included a relatively small number of patients, and dye type was not consistent (indocyanine green [ICG] and/or methylene blue) [10,11].

In the current study, we analyzed a large series of patients with EC treated with SLN biopsy after intraoperative cervical injection of ICG, with the aim of identifying potential patient- or disease-related predictors of unsuccessful SLN mapping.

2. Methods

This study was approved by the Mayo Clinic Institutional Review Board, and only patients who consented to the use of their medical records for research were included. Patients with apparent early-stage EC undergoing SLN biopsy with cervical injection of ICG dye at Mayo Clinic, Rochester, Minnesota, between June 12, 2014, and June 27, 2016, were retrospectively identified from our patient database. Before June 12, 2014, methylene blue was used instead of ICG. Patients who received neoadjuvant treatment, who had International Federation of Gynecology and Obstetrics (FIGO) stage IV disease, who had any synchronous invasive cancer, or for whom SLN mapping was attempted but no nodes were actually searched were excluded.

All patients underwent staging with total hysterectomy, salpingo-oophorectomy, and SLN biopsy by 1 of 8 surgeons. Surgical approach (robotic-assisted, vaginal, laparoscopic, or open abdominal) was individualized on the basis of surgeon preference and patient characteristics. For robotic, laparoscopic, and open abdominal cases, the cervical stroma was injected with ICG after the induction of general anesthesia and before abdominal entry, according to Mayo Clinic internal protocol. The vaginal cases began with an identical cervical stromal injection, followed by a vaginal hysterectomy and salpingo-oophorectomy. If the patient was deemed to be "high risk" per Mayo Clinic Criteria on the basis of frozen section assessment of the uterus (myometrial invasion ≥50%, tumor diameter ≥2 cm, FIGO grade 3, or type 2 histology), abdominal trocars were placed and SLN identification pursued [12]. For injection, 25 mg ICG powder was dissolved in 20 mL of sterile water. Dye was initially injected into the cervix at the 3- and 9-o'clock positions: 1 mL superficial and 1 mL deep at each site, and later injected only superficially for a total of 3 to 4 mL, with a small-caliber needle (22 gauge). This injection was performed by the surgeon or a resident or fellow under the surgeon's supervision. In our practice, retroperitoneal spaces are systematically and thoroughly developed per the National Comprehensive Cancer Network algorithm to remove the SLNs and identify any enlarged lymph nodes.

A *successful procedure* was defined as bilateral mapping of SLNs after ICG injection. An *unsuccessful procedure* included unilateral or no SLN mapping. During surgical exploration, all enlarged (≥2 cm) lymph nodes were removed. If the procedure failed (unsuccessful procedures), side-specific lymphadenectomy was performed in patients at high risk for lymph node metastasis, after intraoperative evaluation of the uterus with frozen section analysis. Patients were defined as "high risk" according to Mayo Clinic criteria reported above [12]. Paraaortic lymphadenectomy was performed in the case of deep myometrial invasion or high-grade histologic type. For unsuccessful procedures in low-risk patients (according to Mayo Clinic criteria), side-specific lymphadenectomy was omitted [13].

Ultrastaging of SLNs followed standard Mayo Clinic protocol. SLNs were bivalved and submitted entirely for frozen section examination. If the lymph node did not show metastatic carcinoma on frozen section, 3 hematoxylin-eosin levels 50 μm apart were obtained after formalin fixation and paraffin embedding. One level was also obtained between these for immunohistochemical staining using anti-cytokeratin AE1/AE3 antibody (Ventana Medical Systems, Inc.).

Demographic, clinical, disease, and surgical characteristics, as well as preoperative and intraoperative parameters, were abstracted from the electronic health record. Patient data included age, BMI, history of prior pelvic or cervical surgery, and history of vaginal or cesarean delivery. Surgical characteristics included volume of dye injected, surgical approach, operative time, and presence of enlarged lymph nodes. Lysis of adhesions was noted if the surgeon's operative report described surgical procedures necessary to remove abdominopelvic scar tissue before beginning the planned operation. Pathologic characteristics of disease abstracted were histologic type, FIGO stage, FIGO grade, tumor diameter, myometrial invasion, cervical stromal invasion, lymphovascular space invasion (LVSI), presence of fibroids, presence of adenomyosis, and uterine weight. The definition of positive lymph nodes included the presence of macrometastasis, micrometastasis, or isolated tumor cells.

2.1. Statistical analysis

Continuous variables were described using mean (SD) or median (interquartile range). Categorical variables were reported as frequency and percentage. The 2-year calendar period was divided into 8 quarters on the basis of standard calendar quarters (January–March [Q1]; April–June [Q2]; July–September [Q3]; October–December [Q4]), starting with Q3 of 2014 (which also included June 2014) and ending with Q2 of 2016. The trend over calendar quarters in the proportion of patients with a successful procedure was evaluated by fitting a logistic regression model. The Pearson correlation coefficient was used to assess the relationship between operative time and date of the procedure. Variables were evaluated for their association with an unsuccessful procedure based on fitting univariate logistic regression models. A parsimonious multivariable logistic regression model was identified using stepwise and backward variable selection methods; variables with $P < .05$ were retained in the final model. Associations were summarized as odds ratio (OR) and 95% CI estimated from the model parameters. P values <.05 were considered statistically significant. Statistical analysis

was performed using the SAS version 9.4 software package (SAS Institute, Inc.).

3. Results

During the study period, 327 patients met the inclusion criteria and their data were analyzed (Fig. 1). Demographic, clinical, surgical, and pathologic characteristics are summarized for the overall group in the Table 1. The mean (SD) age at surgery was 64.2 (10.3) years, and the mean BMI was 34.5 (8.3) kg/m^2. Most patients (91.1%) underwent staging via robotic surgery. Patients had either type 1 ($n = 276$, 84.4%) or type 2 ($n = 51$, 15.6%) EC, including serous, clear cell, carcinosarcoma, and mixed histologic type.

Among the 327 patients, 256 (78.3%) had a successful procedure, with bilateral SLN mapping. Among the other 71 patients (21.7%) who had an unsuccessful procedure, 49 had unilateral mapping (15.0%) and 22 had no mapping (6.7%); of these 71 patients, 57 (80.3%) were defined as having "high risk" EC by frozen section of the uterus, and 14 had low risk. In the 57 high-risk patients with an unsuccessful procedure, 32 underwent side-specific pelvic lymphadenectomy, 13 underwent both pelvic and paraaortic lymphadenectomy, and 12 patients who would have qualified for staging under our institutional algorithm did not undergo lymphadenectomy because of intraoperative clinical conditions, morbid obesity, or poor overall health status. For the 14 low-risk patients with an unsuccessful procedure, 12 did not undergo side-specific lymphadenectomy. Adjuvant treatment was not administered to any of these 14, and no recurrence of disease was registered after a median follow-up of 23.9 months.

The proportion of patients with a successful procedure increased over the 2-year study period (8 quarters), from 57.7% to 83.3% ($P = .06$, test for linear trend) (Fig. 2 A), which may indicate a learning curve for the procedure among the providers. The mean (SD) operative time decreased from 164 (55) minutes in the first quarter to 137 (37) minutes in the last quarter (Fig. 2 B). The Pearson correlation coefficient for the relationship between operative time and date of the procedure was −0.24 ($P < .001$), which suggests that the mean operative time tended to decrease along with increased successful procedures, and therefore fewer lymphadenectomies were performed.

In the analysis of potential predictors of unsuccessful procedure, patients with an unsuccessful procedure were more likely to be older, with a mean (SD) age of 67.0 (9.2) vs 63.5 (10.5) years (OR, 1.41 per 10-year increase in age; 95% CI, 1.08–1.84; $P = .01$) (Table 1). No other baseline demographic or clinical characteristics were associated with unsuccessful procedure. The type of surgical approach (robotic vs vaginal hysterectomy) also was not associated with unsuccessful procedure. Patients with lysis of adhesions at the beginning of surgery (OR, 3.23; 95% CI, 1.66–6.28; $P < .001$) and patients with an intraoperative finding of enlarged lymph nodes (OR, 5.03; 95% CI, 2.00–12.69; $P < .001$) were more likely to have an unsuccessful procedure. The analysis of pathologic characteristics (uterine weight, tumor diameter ≥2 cm, myometrial invasion ≥50%, LVSI, FIGO stage III, FIGO grade 3, histologic type, high-risk disease, presence of fibroids, or adenomyosis) showed no statistically significant associations with unsuccessful procedure. The presence of lymph node metastasis was not associated with unsuccessful procedure ($P = .17$); however, among patients with an unsuccessful procedure, the presence of enlarged lymph nodes predicted nodal metastasis—the proportion with nodal metastasis was 54.5% (6/11) and 6.7% (4/60) among those with and without enlarged lymph nodes, respectively ($P < .001$). Cervical stromal invasion was detected in more patients without versus with a successful procedure (8.5% vs 3.1%), but the difference did not reach statistical significance ($P = .06$). The volume of ICG dye injected also was a predictor of unsuccessful procedure, with a lower success rate if <3 mL of dye was injected (OR, 1.89; 95% CI, 1.10–3.26; $P = .02$).

Multivariable logistic regression models were fit considering the subset of variables with $P < .20$ based on univariate analysis, except for volume of dye injected. Multivariable analysis identified that lysis of adhesions at the beginning of surgery (adjusted OR, 3.07; 95% CI, 1.56–6.07; $P = .001$) and presence of enlarged lymph nodes (adjusted OR, 4.69; 95% CI, 1.82–12.11; $P = .001$) were independent predictors of an unsuccessful procedure.

4. Discussion

The use of SLN mapping as a viable option for EC staging continues to increase, and a high rate of successful mapping decreases the need for side-specific lymphadenectomy with its associated adverse effects. A recent study demonstrated a successful bilateral mapping rate of 79%, but few analyses have addressed the reasons for an unsuccessful procedure and how to address them [14]. Our large, single-institution series

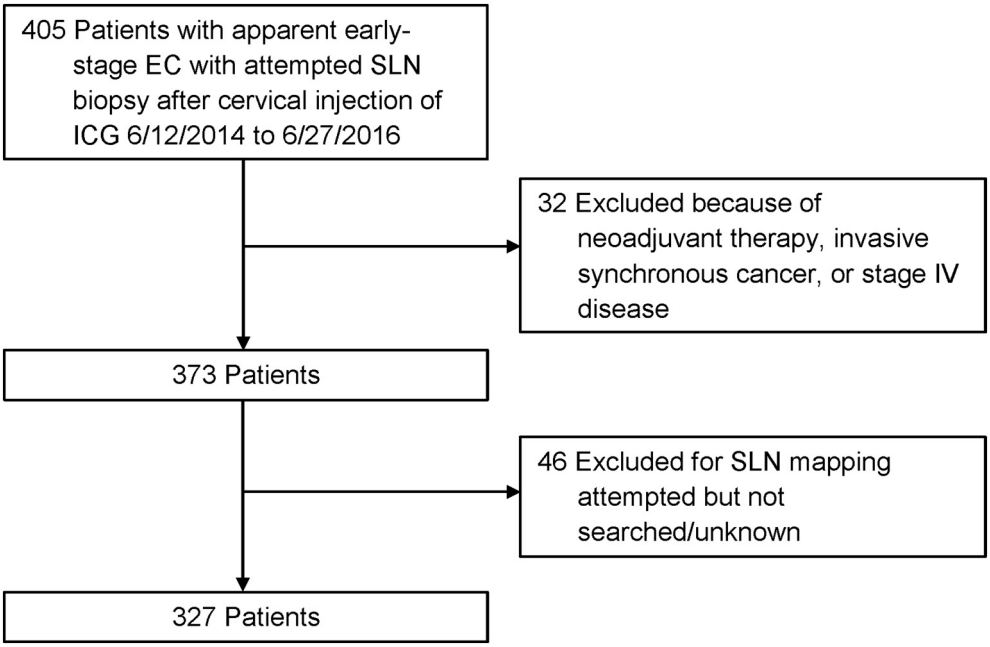

Fig. 1. Selection of Study Patients. EC indicates endometrial cancer; ICG, indocyanine green; SLN, sentinel lymph node.

Table 1
Univariate analysis of predictors of unsuccessful procedure (unilateral or no sentinel lymph node mapping).

Characteristic	Overall (N = 327)[a]	Unsuccessful procedure (n = 71)[a]	Successful procedure (n = 256)[a]	Unadjusted OR (95% CI)	P value[b]
Demographic and clinical					
Age at surgery, y	64.2 (10.3)	67.0 (9.2)	63.5 (10.5)	1.41 (1.08–1.84) (per 10-y increase)	.01
BMI, kg/m^2	34.5 (8.3)	35.4 (8.6)	34.2 (8.3)	1.09 (0.93–1.27) (per 5-unit increase)	.31
Obese (BMI ≥30 kg/m^2)	215 (65.7)	51 (71.8)	164 (64.1)	1.43 (0.80–2.55)	.22
Prior cervical surgery	4 (1.2)	2 (2.8)	2 (0.8)	3.68 (0.51–26.61)	.20
Prior pelvic surgery	84 (25.7)	15 (21.1)	69 (27.0)	0.73 (0.39–1.37)	.32
Vaginal delivery	222 (67.9)	53 (74.6)	169 (66.0)	1.52 (0.84–2.75)	.17
Cesarean delivery	38 (11.6)	10 (14.1)	28 (10.9)	1.34 (0.62–2.90)	.47
Surgical					
Surgical approach					.43
Robotic	298 (91.1)	63 (88.7)	235 (91.8)	Ref	
Vaginal	25 (7.6)	7 (9.9)	18 (7.0)	1.45 (0.58–3.63)	
Open	3 (0.9)	0 (0)	3 (1.2)	NA	
Laparoscopic	1 (0.3)	1 (1.4)	0 (0)	NA	
Lysis of adhesions	45 (13.8)	19 (26.8)	26 (10.2)	3.23 (1.66–6.28)	<.001
Volume of dye injected <3 mL	169 (53.0) (n = 319)	41 (59.4) (n = 69)	109 (43.6) (n = 250)	1.89 (1.10–3.26)	.02
Enlarged lymph nodes	20 (6.1)	11 (15.5)	9 (3.5)	5.03 (2.00–12.69)	<.001
Pathologic					
Uterine weight, g	120 (90–180)	125 (90–185)	115 (90–180)	1.11 (0.81–1.51) (per doubling in weight)	.52
Tumor diameter ≥2 cm	255 (78.0)	55 (77.5)	200 (78.1)	0.96 (0.51–1.81)	.90
Myometrial invasion ≥50%	61 (18.7)	14 (19.7)	47 (18.4)	1.09 (0.56–2.12)	.79
Cervical stromal invasion	14 (4.3)	6 (8.5)	8 (3.1)	2.86 (0.96–8.54)	.06
LVSI	46 (14.2) (n = 325)	13 (18.3)	33 (13.0) (n = 254)	1.50 (0.74–3.04)	.26
FIGO stage III (vs I/II)	30 (9.2)	8 (11.3)	22 (8.6)	1.35 (0.57–3.18)	.49
FIGO grade 3	78 (23.9)	17 (23.9)	61 (23.8)	1.01 (0.54–1.86)	.98
Endometrioid histology (type 1)	276 (84.4)	56 (78.9)	220 (85.9)	0.61 (0.31–1.19)	.15
High risk[c]	271 (82.9)	57 (80.3)	214 (83.6)	0.80 (0.41–1.56)	.51
Positive lymph nodes[d]	32 (9.8)	10 (14.1)	22 (8.6)	1.74 (0.78–3.88)	.17
Presence of fibroids					.25
None	169 (51.7)	32 (45.1)	137 (53.5)	Ref	
<3 cm	123 (37.6)	28 (39.4)	95 (37.1)	1.26 (0.71–2.23)	
≥3 cm	35 (10.7)	11 (15.5)	24 (9.4)	1.96 (0.87–4.41)	
Adenomyosis	88 (26.9)	16 (22.5)	72 (28.1)	0.74 (0.40–1.38)	.35

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; NA, not applicable; OR, odds ratio; Ref, reference.
[a] Values are mean (SD), No. of patients (%), or median (interquartile range).
[b] Variables were evaluated for their association with unsuccessful procedure based on fitting univariate logistic regression models.
[c] High risk defined as tumor diameter ≥2 cm, myometrial invasion ≥50%, FIGO grade 3, or type 2 histology.
[d] Positive nodes on sentinel lymph node biopsy or pelvic or paraaortic lymphadenectomy.

analyzing consecutive patients with apparent early-stage EC suggests several predictors of an unsuccessful procedure in women undergoing SLN biopsy for EC staging. These include older age, need for lysis of adhesions at the beginning of surgery, cervical stromal invasion, and the presence of enlarged lymph nodes. Of these, presence of enlarged lymph nodes and lysis of adhesions at the beginning of surgery were identified as independent risk factors, which suggests a need for careful management among patients with these findings. In addition to predictors of unsuccessful procedure, the study also showed that increasing expertise of the surgeon may contribute to increased successful procedures. In the analysis with stratification by calendar quarter, the rate of successful procedures increased from 57.7% in the first quarter to 83.3% in the final quarter. This coincides with a significant decrease in operative time and concurs with previous investigations showing that surgeon experience is an independent factor affecting the rate of successful procedures [15].

Previous investigations have demonstrated that a high BMI is associated with a higher likelihood of unsuccessful procedure, an important finding because obesity is one of the most important risk factors for EC [10,11]. This series did not show a significant association between BMI and unsuccessful procedure; however, our cohort had a high percentage of patients with obesity (65.7% with a BMI ≥30 kg/m^2).

Among patient characteristics, older age was a predictor of unsuccessful procedure (OR per 10-year increase in age, 1.41; 95% CI, 1.08–1.84; P = .01). This finding is similar to that in reports of SLN mapping in breast cancer patients and may be caused by increased fibrotic and fatty tissue with age, which thus decreases lymphatic flow [16,17]. The presence of grossly enlarged lymph nodes at the time of surgery was independently associated with unsuccessful procedure. This validates work by Tanner et al. [10] and may be explained by either the full development of avascular spaces, which occurs with full lymphadenectomy, or blocked lymphatic flow, as can occur with gross lymphatic metastases. In our series, 55% of patients (6/11) with enlarged lymph nodes and an unsuccessful procedure had metastatic disease, and all of them had high-grade histologic type and/or deep myometrial infiltration. Thus, even if a correlation between failed mapping and metastatic disease has not yet been demonstrated, the presence of enlarged lymph nodes should be considered a risk factor for metastatic disease, especially in patients with high-risk features and an unmapped pelvis.

We observed no significant associations between tumor pathologic characteristics and bilateral mapping. The failure of the procedure is therefore independent of tumor diameter, grade, myometrial invasion, histologic type, LVSI, uterine weight, presence of fibroids, or positive lymph nodes. However, patients with cervical stromal invasion were slightly more likely to have an unsuccessful procedure.

Strengths of our study include analysis of a large group of consecutive patients undergoing surgery for EC at a single institution with a uniform approach to care. Limitations include its retrospective nature and lack of systematic preoperative imaging, which could have more objectively identified enlarged lymph nodes and thus stratified risk.

Although surgical and pathologic characteristics that increase the risk of an unsuccessful procedure cannot be changed (need for lysis of adhesions, enlarged lymph nodes, age, cervical stromal invasion), some factors can be optimized to secure the highest successful

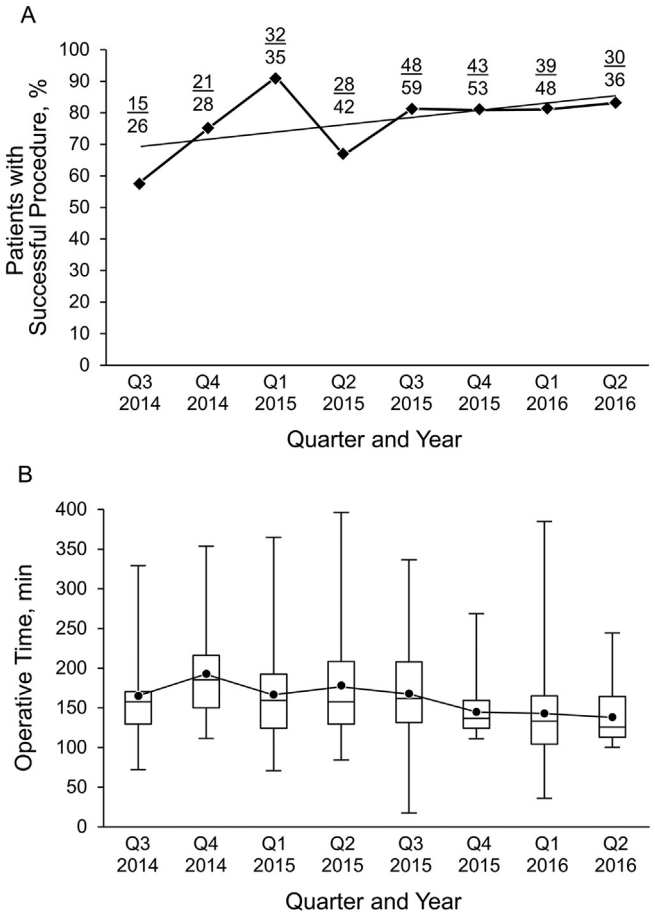

Fig. 2. Outcome Measures by Quarter (June 2014 through May 2016). A, Proportion of patients with a successful procedure. Fractions indicate number of successful procedures over total procedures. Straight line denotes the linear trend line. B, Operative time. Box plots show median, interquartile range, and 95% CI; dots indicate mean. Q indicates quarter.

procedure rate possible. Because lysis of adhesions was an independent predictor of unsuccessful procedure and most likely results from increased operative time before SLN identification and/or presence of scar tissue in the pelvis from prior pelvic surgery that limits lymphatic flow, delaying cervical dye injection until completion of lysis of adhesions could be considered in these patients.

The experience of the surgeon regarding technical and surgical issues and adherence to a standardized injection protocol ensure an improved rate of successful procedure. At our institution, several surgeons were learning the technique, including new staff physicians, residents, and fellows. It has been noted that deep cervical stromal injection of ICG can generate excessive fluorescent signal in the parametrium and retroperitoneum and, thus, may lead to an unsuccessful procedure despite fluorescent mapping. We have no information regarding injection depth in our data set, but our practice has moved away from deep injections, favoring superficial cervical injections only.

In select cases, the use of preoperative imaging could help to identify patients with enlarged lymph nodes who are at increased risk for an unsuccessful procedure; those with an unsuccessful procedure and high-risk features must undergo lymph node dissection to avoid understaging. For low-risk patients, we suggest frozen section of the uterine specimen and avoidance of completion lymphadenectomy on the basis of Mayo Clinic criteria, a belief shared by others in our field [18]. We believe that optimizing the rate of bilateral SLN detection is critical to further decreasing the number of lymphadenectomies required for proper EC staging and, thus, the amelioration of morbidity related to this procedure.

Acknowledgments

Role of the funding source

This project did not receive any funding from external sources.

Author contributions

Conceived and designed the study: L.T., A.M., G.G., A.W., and M.M.
Collected and analyzed data: J.C., F.M., S.C., C.L., G.K., A.K., L.T., A.M., G.G., A.W., and M.M.
Reviewed the pathologic biospecimen: G.K.
Helped with writing first draft of manuscript: L.T., A.M., M.M., G.G., and A.W.
Provided critical insight and revision to manuscript: All authors.

Declaration of competing interest

All authors report no conflicts of interest to disclose.

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