



Case series

The role of secondary full lymphadenectomy for patients with early-stage endometrial cancer and isolated tumor cells detected on sentinel lymph node biopsy

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ARTICLE INFO

Keywords:

Endometrial cancer
Sentinel lymph node
Isolated tumor cells
Micrometastases
Secondary lymphadenectomy

ABSTRACT

Sentinel lymph node (SLN) mapping is a surgical technique with high accuracy in detecting metastases while limiting morbidity associated with full lymphadenectomy in endometrial cancer. Recent retrospective data suggests that recurrence risk is low for patients with isolated tumor cells (ITCs). The objective of this study was to describe the pathologic findings, postoperative complications, and outcomes of endometrial cancer patients with ITCs who subsequently underwent a second surgical procedure, full lymph node dissection (LND) following initial staging surgery.

All patients with clinically early stage endometrial cancer who underwent planned minimally invasive surgical staging with SLN biopsy demonstrating ITCs at a single institution from 1/1/2017 to 12/31/2020 were identified retrospectively.

Six patients with endometrial cancer with ITC who subsequently underwent secondary full LND were identified. Half of patients experienced postoperative complications within 30 days after LND, including persistent thigh numbness, a urinary tract infection, and a presyncopal episode. No patients had a change in stage as a result of subsequent full LND. One patient received no adjuvant therapy, while 83.3 % (5/6) received vaginal brachytherapy. One patient experienced distal recurrence six months after completing brachytherapy, while five remain without evidence of disease on most recent follow-up.

In patients who underwent completion lymphadenectomy for ITCs identified during initial surgical staging for endometrial cancer, no additional lymph node metastatic disease was identified. This study supports current data there is a limited role for additional lymph node assessment in patients with early stage endometrial cancer with ITCs identified on SLN biopsy.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States with an estimated incidence of 66,570 cases in 2021 (Abu-Rustum et al., 2021). Mortality rates from endometrial cancer continue to increase over recent decades (Giaquinto et al., 2022). The majority of patients diagnosed with endometrial cancer have uterine-confined disease at the time of diagnosis (Creasman et al., 1987). Surgical staging for apparent uterine-confined endometrial cancer consists of total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Since 2018, the National Comprehensive Cancer

Network (NCCN) guidelines for Uterine Cancer state that assessment of lymph node status can consist of full pelvic lymph node dissection (LND) with or without *para*-aortic LND or sentinel lymph node (SLN) biopsy (Abu-Rustum et al., 2021). The use of SLN biopsy has increased in recent years due to high diagnostic accuracy in the detection of nodal metastases and decreased surgical morbidity (Rossi et al., 2017).

SLN evaluation incorporates specific surgical and pathologic protocols.

Advances in pathologic analysis via ultrastaging have allowed for the detection of low-volume metastases, including micrometastases and isolated tumor cells (ITC). The diameter-based classification system of

Abbreviations: ITC, Isolated tumor cell; SLN, sentinel lymph node; LND, lymph node dissection.

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<https://doi.org/10.1016/j.gore.2022.101074>

Received 8 August 2022; Received in revised form 26 September 2022; Accepted 28 September 2022

Available online 30 September 2022

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metastatic neoplastic cell clusters is derived from breast cancer literature: macrometastases measure >2 mm, micrometastases are 0.21–2 mm, and ITCs measure ≤0.2 mm (McCready et al., 2004). However, there is a paucity of data regarding the significance and management of ITCs, and most available studies are retrospective. Although initial studies described sequential SLN dissection followed by full lymphadenectomy during the same surgery, these protocols were developed to define the sensitivity and specificity of this technique. One management question that remains unclear from available studies is whether a secondary surgery for full lymphadenectomy is indicated when ITCs are identified during SLN biopsy.

The objective of this study was to describe the pathologic findings, postoperative complications, and outcomes of endometrial cancer patients with ITCs identified on SLN biopsy who subsequently underwent a second surgical procedure for full LND.

2. Materials and methods

This was a case series of retrospectively collected data. After IRB approval was obtained, all patients with clinically early-stage endometrial cancer who underwent planned minimally invasive surgical staging with SLN biopsy at a single institution between 1/1/2017 and 12/30/2020 were identified retrospectively. All patients included underwent SLN biopsy in accordance with NCCN guidelines. All patients received injections of ICG dye into the cervical stroma at the 3 and 9o'clock positions, superficially and 1 cm deep into the stroma, with some surgeons opting for 4 quadrant injections. SLN mapping was identified in each hemipelvis with the use of the SPY laparoscope or using the Firefly in robotic cases. If mapping did not occur at the time of initial assessment, pelvic and para-aortic lymphadenectomy were performed at the discretion of the surgeon. Patients with ITCs identified on SLN biopsy who subsequently underwent subsequent secondary procedure for completion full LND were identified. Demographic, clinicopathologic, treatment and outcome data were collected through electronic medical record review. Surgical procedure information, 30-day postoperative complications from initial and secondary surgeries, as well as long-term complications and outcomes were identified. All postsurgical complications were assessed according to the Clavien-Dindo Grading System (Clavien et al., 2009).

3. Results

A total of 848 endometrial cancer patients who underwent minimally invasive surgical staging with SLN biopsy were identified. Thirty-three (3.9 %) had ITCs on SLN biopsy. Among the patients with ITCs, the mean age was 65 years (range 38–85), and the mean body mass index (BMI, kg/m²) was 38 (range 17.6–67.9). All patients were white.

Six patients with ITCs (18.2 %) underwent a secondary procedure for completion full LND and twenty-seven patients (81.8 %) did not undergo completion LND (Table 1). The recommendation for completion lymphadenectomy in some patients was based upon a multidisciplinary tumor board recommendation and provider preference. The mean time between initial staging surgery and secondary procedure for full LND was 34.6 days (range 19–56 days). Four of these patients underwent bilateral pelvic and paraaortic LND, and two underwent bilateral pelvic LND only. All completion full LNDs were performed via a minimally invasive approach, with five being laparoscopic and one robotic-assisted. Four patients were discharged the day of surgery, and two were discharged on postoperative day one.

All patients with ITCs who underwent subsequent full LND had grade 1 (50 %) or grade 2 (50 %) endometrioid adenocarcinoma histology. Three patients had stage IA disease, two had stage IB, and one had stage II disease. Of these six patients, five (83 %) had high risk tumor features based on Mayo criteria (Table 2). The average number of non-sentinel lymph nodes analyzed per patient was 7.5 (range 4–11). Four patients had lymphovascular space infiltration (LVSI) (66.7 %).

Table 1
Patient characteristics.

	Patients who underwent completion lymphadenectomy (n = 6)	Patients with ITC who did not undergo completion LAD (n = 27)
Age (years), mean (range)	66 (54–77)	65 (38–85)
Race, n (%)	6	27
White	6 (100 %)	27 (100 %)
Body Mass Index, mean (range)	33.1 (26.2–37.7)	39.07 (17.6–67.9)
<i>Clinical stage, n (%)</i>		
Stage		
IA	3 (50 %)	8 (30 %)
IB	2 (33 %)	15 (56 %)
II	1 (17 %)	2 (7 %)
IIIA	0 (0 %)	2 (7 %)
<i>Histology, n (%)</i>		
Adenocarcinoma		
Mixed Serous and Endometrioid Adenocarcinoma	6 (100 %)	24 (88 %)
Mixed Clear Cell and Serous	0 (0 %)	1 (4 %)
Carcinosarcoma	0 (0 %)	1 (4 %)
<i>Surgical Approach-Full Lymph Node Dissection</i>		
Laparoscopic	5 (83 %)	22 (81 %)
Robotic	1 (17 %)	5 (19 %)
<i>Full Lymph Node Dissection at time of initial procedure</i>		
Yes	0	2 (7 %)
No	6 (100 %)	25 (93 %)
<i>Lymph Node Dissection</i>		
Pelvic only	2	2
Pelvic and Paraaortic	4	0
<i>Recurrence</i>		
No	5 (83 %)	26 (96 %)
Yes	1 (17 %)	0
Progressive disease	0	1 (4 %)

Table 2
Clinical and pathologic characteristics of patients undergoing secondary lymphadenectomy.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	61	56	54	71	77	72
Depth of Invasion	6	18	80	55	70	27
Presence of LVSI	0	0	1	1	1	1
Tumor Grade	1	1	2	2	2	1
Tumor Maximum dimension (cm)	4	1.5	10	4.7	4.5	5.5

Following completion full LND, no patients had additional lymph node metastases identified on pathologic analysis. One patient had no adjuvant therapy, and the remaining five patients received vaginal cuff brachytherapy. No patients received adjuvant chemotherapy or external beam radiation therapy. One patient with stage 1B disease (age 71 years, grade 2, depth of myometrial invasion 55 %, and positive LVSI) experienced distant recurrence with abdominal wall, vulvar, labial, and

pelvic lymph node metastases noted six months after completing brachytherapy. The remaining five patients were without evidence of disease on most recent follow-up (median follow up time 21.5 months, range 5.9–32.4 months). Among the 27 patients in our cohort with ITCs who did not undergo a subsequent completion lymphadenectomy, no patients experienced disease recurrence; however, one patient with Stage IIIA carcinosarcoma experienced disease progression and subsequently died as a result of uterine cancer. This patient completed one cycle of adjuvant carboplatin and taxol but discontinued chemotherapy due to poor tolerance and declined radiation therapy.

Three of the patients who underwent secondary full LND experienced 30-day postoperative complications following completion LND, in comparison to no complications following initial staging surgery in this group. These complications included lateral thigh numbness (Clavien Dindo grade 1), a urinary tract infection treated with antibiotics (Clavien Dindo grade 1) and a sprained ankle requiring radiologic imaging following a pre-syncope episode in the postoperative recovery area (Clavien Dindo grade 1). Of the patients with ITCs who did not undergo a secondary full LND, there was a single patient who experienced multiple postoperative complications: an incarcerated incisional hernia requiring exploratory laparotomy, small bowel resection/reanastomosis, and bilateral pulmonary emboli with intensive care unit admission (Clavien Dindo grade 4).

4. Discussion

In this case series, endometrial cancer patients with SLN ITCs who underwent completion full LND at a second surgery had no additional nodal metastases, and these patients experienced more postoperative complications. Although all complications were mild, given the limited prognostic contribution and added morbidity of these procedures, our data suggest lack of clinical benefit of returning to the operating room for completion lymphadenectomy in patients with positive ITCs.

In recent years, SLN biopsy has become widely accepted as a surgical technique for lymph node assessment during the surgical staging of clinically early-stage endometrial cancer. The FIRES trial demonstrated that SLN dissection offers a technique with high sensitivity and low false negative rate for metastatic disease while minimizing the surgical morbidity associated with full LND (Rossi et al., 2017). Ultrastaging of SLNs allows for the identification of low volume metastases, including ITCs (Backes et al., 2021). However, the significance of ITCs in patient prognosis and adjuvant treatment decisions remains unclear due to the rarity of ITCs and limited long-term data. In the FIRES trial, nodal metastases in SLN were categorized into high or low-volume metastatic disease. Both ITCs and micrometastases identified on ultrastaging were included in the low-volume nodal metastases category. In that cohort, six of 21 patients with low-volume nodal metastases were noted to have further metastases on subsequent full LND. However, it is difficult to draw conclusions regarding the significance of SLN ITCs and the risk of additional lymph node metastases given the small number of patients with low volume metastases and the fact that micrometastases and ITCs were grouped together (Rossi et al., 2017).

A recent retrospective study of 175 patients with SLN ITCs in otherwise stage I or II endometrioid adenocarcinoma found no significant difference in recurrence free survival regardless of adjuvant therapy (Backes et al., 2021). Of the 175 patients in the cohort, 85 patients underwent SLN biopsy followed by completion full LND (pelvic +/- para-aortic) at the time of initial surgical staging. However, patients in this study were excluded if they had evidence of micrometastases or macrometastases in any lymph node, so the risk of other metastases in patients with SLN ITCs is unclear from this data.

In the present study, of the six patients with SLN ITCs who underwent secondary procedure for full LND, none of the non-SLNs obtained demonstrated metastatic disease. Moreover, half of the patients who

underwent a secondary procedure experienced a mild postoperative complication (Clavien Dindo grade 1). Given accumulating data that SLN dissection is a viable technique with high negative predictive value, our study suggests that completion LND in the setting of SLN ITCs does not have clinical utility and may be associated with additional surgical morbidity.

There are clear limitations to our study. This is a retrospective, single institution case series. The sample size is small, and the follow-up is limited. However, to our knowledge, this is the first study to report on the postoperative outcomes of patients with SLN ITC who underwent return to the operating room for completion LND.

The appropriate treatment for patients with endometrial cancer who are found to have positive SLN ITCs remains to be completely defined as we gain more data on patients prospectively. Our report suggests that secondary surgery to perform complete lymphadenectomy has no additional prognostic significance and may present more risk, so should not be performed.

Informed Consent

Informed consent was obtained from all individual participants for who identifying information is included in this article.

Author Contribution

Dr. Brigid Mumford is the corresponding author of the case series, and the contributing authors are Dr. Alison Garrett and Dr. Jamie Lesnock. All authors have made a significant contribution to this report, and all authors have read and approved the final version submitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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