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MULTICENTER STUDY COMPARING ONCOLOGIC OUTCOMES BETWEEN TWO NODAL ASSESSMENT METHODS IN PATIENTS WITH DEEPLY INVASIVE ENDOMETRIOID ENDOMETRIAL CARCINOMA: A SENTINEL LYMPH NODE ALGORITHM VERSUS A COMPREHENSIVE PELVIC AND PARAAORTIC LYMPHADENECTOMY

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Abstract

Objectives: To compare oncologic outcomes in the staging of deeply invasive endometrioid endometrial carcinoma (EEC) using a sentinel lymph node algorithm (SLN) versus pelvic and paraaortic lymphadenectomy to the renal veins (LND); to compare outcomes in node-negative cases.

Methods: At two institutions, patients with deeply invasive (>50% myometrial invasion) EEC were identified. One institution used LND (2004-2008), the other SLN (2005-2013). FIGO stage IV cases were excluded. Clinical characteristics and follow-up data were recorded.

Results: 176 patients were identified (LND, 94; SLN, 82). SLN patients were younger ($p=0.003$) and had more LVSI ($p<0.001$). 9.8% in the SLN and 29.8% in the LND cohorts, respectively, received no adjuvant therapy ($p<0.001$). There was no association between type of assessment and recurrence; adjusted hazard ratio (aHR; LND vs. SLN) 0.87 (95% CI 0.40, 1.89) PFS. After controlling for age and adjuvant therapy, there was no association between assessment method and OS (aHR 2.54; 95% CI 0.81, 7.91). The node-negative cohort demonstrated no association between survival and assessment method: aHR 0.69 (95% CI 0.23, 2.03) PFS, 0.81 (95% CI 0.16, 4.22) OS. In the node-negative cohort, neither adjuvant EBRT+/-IVRT (HR 1.63; 95% CI 0.18, 14.97) nor adjuvant chemotherapy+/-EBRT+/-IVRT (HR 0.49; 95% CI 0.11, 2.22) were associated with OS, compared to no adjuvant therapy or IVRT-only.

Conclusion: Use of an SLN algorithm in deeply invasive EEC does not impair oncologic outcomes. Survival is excellent in node-negative cases, irrespective of assessment method. Adjuvant chemotherapy in node-negative patients does not appear to impact outcome.

Keywords

Sentinel lymph node algorithm; Endometrial cancer; High-risk; Deep invasion

BACKGROUND

The extent of lymph node assessment in the surgical management of endometrial carcinoma remains a topic of debate. The management of lymph nodes ranges from no lymphadenectomy (LND), based upon tumor characteristics at frozen section, to full pelvic and paraaortic LND. Tumors with endometrioid histology, that are clinically confined to the uterus but demonstrate >50% myometrial invasion (i.e. deeply invasive endometrial

carcinomas), have lymph node metastases in approximately 20% of cases; thus, lymph node assessment is more broadly performed in this group [1, 2].

There is no agreement regarding the method of lymph node assessment in patients with deeply invasive endometrial carcinoma. Full pelvic and paraaortic nodal dissection has been advocated, but data has shown that the rate of symptomatic lymphedema increases when 10 lymph nodes are removed [3]. Sentinel lymph node (SLN) assessment is another proposed option which has gained popularity, and for which there is an increasing amount of supportive data; in 2018 it was added to the National Comprehensive Cancer Network guidelines [4]. In tumors with endometrioid histology and limited myometrial invasion, the use of an SLN algorithm, compared to selective nodal assessment based on tumor characteristics, has shown a higher detection rate of stage IIIC1 disease, and a similar detection rate of stage IIIC2 disease, with no apparent compromise in oncologic outcomes [5]. Recent data demonstrate that detection of stage IIIC1 disease in patients with any grade, deeply invasive endometrioid adenocarcinoma is not adversely affected by SLN assessment when compared to full LND [6]. However, the oncologic outcome of an SLN algorithm compared to full pelvic and paraaortic LND in deeply invasive endometrioid endometrial carcinoma (EEC) has not been reported.

In this study, we compare oncologic outcomes of patients with deeply invasive EEC staged with an SLN algorithm, to oncologic outcomes of patients staged with a full pelvic and paraaortic LND to the renal veins. We also compare outcomes specifically in patients with negative or unassessed lymph nodes.

METHODS

Patients with newly diagnosed, apparently uterine-confined EEC of any grade—excluding stage IV—and 50% myometrial invasion were identified at Memorial Sloan Kettering Cancer Center (MSK) and the Mayo Clinic, using institutional databases. The MSK database (SLN cohort) encompassed the years 2005-2013; the Mayo Clinic database (LND cohort) encompassed the years 2004-2008. During these time periods at these two institutions, the surgical algorithm for endometrial carcinoma staging differed only by method of lymph node assessment. Both cohorts underwent hysterectomy, bilateral salpingo-oophorectomy, and peritoneal cytology. In this population, the surgical algorithm at the Mayo Clinic included full pelvic and paraaortic LND to the renal veins bilaterally, following intraoperative assessment of tumor characteristics. Lymphadenectomy was performed for any patient in whom frozen section evaluation of the uterine specimen demonstrated grade 3 endometrioid histology or any non-endometrioid histology, 50% myometrial invasion, or tumor size >2 cm. At MSK, surgical evaluation included an SLN algorithm per institutional protocol, as previously described [7]. Lymphatic mapping was performed by injecting 4 mL of either blue dye or indocyanine green dye into the deep (1-2 cm) and superficial (1-2 mm) cervical stroma at 3 and 9 o'clock prior to staging. The peritoneal cavity was inspected for evidence of metastatic disease. The retroperitoneum was examined, and any enlarged or suspicious non-sentinel lymph nodes were removed along with the identified sentinel nodes. A full LND was performed on any non-mapping hemipelvis. Due to the retrospective nature of this analysis, and in order to focus only on

patients eligible for SLN dissection (as reported in the MSK cohort), 10 patients with widespread, enlarged positive lymph nodes, evident at preoperative imaging, were eliminated from the Mayo Clinic cohort. Given the timeframe of this study, some patients in the SLN cohort had a back-up LND immediately following excision of the SLNs. In the SLN cohort, patients were considered to have also had an additional LND if >5 lymph nodes were removed from one hemipelvis in addition to the SLN, or if any lymph nodes were removed in a hemipelvis which had no SLNs removed (i.e. a non-mapping hemipelvis). SLN mapping was deemed successful if one or both hemipelvises were mapped.

Excised SLNs were then evaluated using the MSK Pathologic Processing Protocol, also known as “ultrastaging”, which has been previously described [8]. Briefly, this includes standard lymph node assessment via sectioning of the SLN longitudinally, and staining it with hematoxylin and eosin (H&E) to assess for the presence of metastatic tumor cells. If tumor cells are identified, the lymph node is considered positive and no further evaluation is performed. If no tumor cells are identified, the SLN is serially sectioned and stained with both H&E and immunohistochemistry (IHC) for cytokeratin AE1:AE3 to assess for low-volume metastases.

Macrometastasis (defined as any nodal metastasis ≥ 2 mm), micrometastasis (defined as any nodal metastasis >0.2 mm but <2 mm), and isolated tumor cells (ITCs; defined as metastasis <0.2 mm), were considered node-positive. When the tumor measurement was not clearly delineated on the pathology report, and the terms “micrometastases” and “isolated tumor cells” were not used, a determination was made by reviewing the pathology report and seeking clarification with a gynecologic pathologist as needed. Adjuvant therapy was administered per each institution’s guidelines.

Clinical, pathologic, and surgical characteristics were recorded for all patients. Lymphovascular space invasion (LVSI) was defined by pathologists at both centers as tumor cells within or attached to the wall of a capillary-like space. The presence of artifactual tumor displacement was excluded. Date of last follow-up, date of recurrence, and disease status at last follow-up were recorded. Location of first recurrence was recorded and defined as follows: *hematogenous* included locations that metastatic cells could only reach hematogenously (i.e. brain, bone, intraparenchymal liver); *lymphatic* included enlarged lymph nodes or masses in known lymph node basins; *vaginal* included disease involving any portion of the vagina, including the vaginal cuff; *peritoneal* included disease recurring anywhere in the peritoneal cavity or on a peritoneal surface.

Statistical analysis was performed using the SAS version 9.3 software package. Baseline characteristics were compared between the SLN and LND cohorts. The two-sample t-test was used to compare age and body mass index (BMI); the Wilcoxon rank-sum test was used to compare the number of lymph nodes removed; and the Chi-squared test or Fisher’s exact test were used to compare categorical variables. The outcomes of interest were overall survival (OS), progression-free survival (PFS), and non-vaginal PFS. Considering the different time periods encompassed by the two cohorts, follow-up was restricted to the first 3 years following surgery to analyze each time-to-event outcome. Comparisons of outcomes between the SLN and LND cohorts were first evaluated univariately based on fitting

standard Cox proportional hazards regression models, using time since surgery as the time scale. Second, the Cox models were fit using age as the time scale, in order to adjust for the difference in age between the two cohorts. Lastly, the Cox models were further adjusted for adjuvant therapy. Associations were summarized by reporting hazard ratios (HR) and corresponding 95% confidence intervals (CI). The above analyses were applied to all patients combined, and to the subset of patients who had negative lymph nodes or had no lymph node assessment of any kind.

In all patients combined, each clinicopathologic characteristic was evaluated univariately for an association with OS, based on fitting separate stratified Cox proportional hazards models. These models were stratified by cohort (i.e. institution) to allow for a separate baseline hazard function for each cohort. A multivariable analysis, restricted to factors with a combined three degrees of freedom (considering there were 24 deaths), was performed to identify factors associated with OS. Among the subset of patients with negative lymph nodes or no lymph node assessment, additional sets of univariate analyses were performed for each of the outcomes (OS, PFS, and non-vaginal PFS, respectively).

RESULTS

Review of both institutional databases identified 176 patients: 82 in the SLN cohort and 94 in the LND cohort, with any grade EEC and 50% myometrial invasion (excluding stage IV disease). Clinical and pathologic characteristics of each cohort are shown in Table 1. Patients in the SLN cohort were younger than those in the LND cohort (mean age 64.3 ± 10.2 years vs. 69.2 ± 10.9 years, $p=0.003$) and had more LVSI (74.4% vs. 30.9%, $p<0.001$). The distribution of International Federation of Gynecology and Obstetrics (FIGO) stage ($p=0.16$) and grade ($p=0.44$) were not statistically different between the two groups. Adjuvant therapy differed between the two groups: 9.8% in the SLN cohort received no adjuvant therapy, compared to 29.8% in the LND cohort ($p<0.001$).

Lymphadenectomy characteristics are presented in Table 2. Specific details regarding SLN mapping and nodal dissection in the SLN cohort are presented in Figure 1. Pelvic lymph nodes were removed in 98.8% (81/82) of patients in the SLN cohort, compared to 93.6% (88/94) in the LND cohort ($p=0.12$). The median number of pelvic nodes removed in the SLN cohort was 10 (interquartile range [IQR]: 4, 14), compared to 34 in the LND cohort (IQR: 27, 44; $p<0.001$). Among patients with any pelvic lymph nodes removed, positive pelvic lymph nodes were identified in 33.3% (27/81) of the SLN cohort and 14.8% (13/88) of the LND cohort ($p=0.005$). Paraaortic lymph nodes were removed in 34.1% (28/82) of the SLN cohort and 90.4% (85/94) of the LND cohort ($p<0.001$). Among patients who had a paraaortic LND, 10.7% (3/28) in the SLN cohort were found to have positive nodes, compared to 16.5% (14/85) in the LND cohort ($p=0.56$).

Median follow-up time was 2.6 years (IQR: 1.7, 3.6) in the SLN cohort and 2.8 years (IQR: 1.7, 4.3) in the LND cohort. Overall, 32 patients recurred within the first 3 years following surgery; 23 of these recurrences were non-vaginal. There was no statistically significant association between type of nodal assessment and recurrence, with an adjusted hazard ratio (HR) (LND vs. SLN) of 0.87 (95% CI 0.40, 1.89) for PFS and 0.77 (95% CI, 0.30-1.96) for

non-vaginal PFS (Table 3). The association between type of nodal assessment (LND vs. SLN) and death was attenuated after controlling for age and adjuvant therapy (adjusted HR 2.54; 95% CI 0.81-7.91; Table 3).

In considering patients from the two cohorts combined, univariate and multivariable analyses were performed to identify factors associated with OS (Table 4). On multivariable analysis, FIGO stage III (adjusted HR 15.41; 95% CI 5.88, 40.44), and adjuvant therapy (adjusted HR for chemotherapy $\pm$ EBRT $\pm$ IVRT vs. no therapy/IVRT only/unknown 0.10; 95% CI 0.03, 0.31) were associated with OS.

The characteristics of patients with negative lymph nodes or those without lymph node assessment are depicted in Table 5. Patients in the SLN cohort were younger (mean age 64.0 ± 10.2 years vs. 69.4 ± 10.6 years, $p=0.005$) and had more LVSI (62.3% vs. 27.0%, $p<0.001$). Distribution of FIGO grade ($p=0.06$) and stage ($p=0.70$) were not statistically different between cohorts. Pelvic lymph nodes were assessed in 98.1% (52/53) of the SLN cohort and 91.9% (68/74) of the LND cohort ($p=0.24$). Para-aortic LND was performed in 32.1% (17/53) of patients in the SLN cohort compared to 87.8% (65/74) of those in the LND cohort ($p<0.001$). In the SLN cohort 11.3% of patients received no adjuvant therapy, compared to 33.8% in the LND cohort ($p<0.001$).

The comparison of outcomes between the LND and SLN cohorts, among the subset of patients with negative lymph nodes or without lymph node assessment, is summarized in Table 3. After adjusting for age and adjuvant therapy, the adjusted HRs were 0.69 (95% CI 0.23, 2.03), 0.67 (95% CI 0.19, 2.33), and 0.81 (95% CI 0.16, 4.22) for PFS, non-vaginal PFS, and OS, respectively.

In considering patients from both cohorts combined, cervical stromal invasion was the only variable associated with PFS on univariate analysis, with an HR of 3.03 (95% CI: 1.18, 7.81). Both cervical stromal invasion and higher FIGO stage were univariately associated with non-vaginal PFS (Table 6). On univariate analysis, the variables identified as being significantly associated with OS included increasing age (HR 2.53 per 10-year increase in age, 95% CI 1.35, 4.73), LVSI (HR 3.75, 95% CI 1.22, 11.54), positive peritoneal cytology (HR 3.94, 95% CI 1.31, 11.91), and FIGO stage III disease (HR 12.70, 95% CI 3.63, 44.46; Table 6). A multivariable analysis was not performed, given that there were only 14 deaths within the first 3 years among the 127 patients.

Eleven patients (11/53, 20.8%) in the SLN cohort and 11 (11/74, 14.9%) in the LND cohort experienced a recurrence within 3 years, in the subgroup with negative or unassessed lymph nodes. Of these, an equal proportion in each cohort were lymphatic recurrences (4/11, 36.4%). Sites of first recurrence, and specific locations of any lymphatic recurrences in patients in the node-negative/unassessed subgroup, are presented in Table S1.

DISCUSSION

The surgical approach for lymph node assessment in patients with deeply invasive EEC is not uniformly practiced or standardized. Historically, full pelvic and para-aortic LND has been considered the mainstay for evaluation of metastatic disease in patients with

intermediate and high-risk endometrial carcinoma. However, a Society of Gynecologic Oncology (SGO) survey by Soliman et al reported that only 11% of responding clinicians practiced paraaortic dissection to the renal vessels [9]. Other studies have demonstrated increased morbidity with this approach, particularly when 10 pelvic lymph nodes are removed [3, 10]. The SLN approach has recently been investigated as a potentially less morbid method of lymph node assessment in apparent early stage endometrial carcinoma [5, 7, 11]. Previously published data supports the efficacy and oncologic safety of an SLN algorithm in EEC with limited myometrial invasion [5, 12], but few reports have evaluated its efficacy and safety in the setting of deeply invasive endometrioid histology. Even with an increased risk of nodal metastases of approximately 20% in patients with deeply invasive EEC [2, 13], Ducie et al have shown a comparable detection rate of stage IIIC1 between comprehensive pelvic and paraaortic LND (23.4%) and the SLN algorithm (32.9%, $p=0.14$) used in this study [6]. We know of no previously published data comparing routine pelvic and paraaortic LND versus an SLN algorithm with respect to oncologic outcomes in deeply invasive EEC. We demonstrate similar oncologic outcomes with the use of a SLN algorithm compared to full pelvic and paraaortic LND, in a group of patients at increased risk of nodal metastasis.

Concern has been expressed regarding the lack of routine evaluation of the paraaortic nodal basin with an SLN algorithm using cervical dye injection [14]. Approximately 4% of SLNs identified using cervical dye injection are in the paraaortic nodal basin [15], and the SLN algorithm utilized in our study includes removal of any non-sentinel suspicious lymph nodes identified, leading to a paraaortic LND in 34.1% of the SLN cohort in our study. In a similar cohort, Ducie et al demonstrated an increased detection rate of metastatic paraaortic lymph nodes in patients undergoing full pelvic and paraaortic LND, compared to patients undergoing SLN assessment [6]. The clinical importance of this finding is uncertain. The SEPAL trial demonstrated an increased risk of paraaortic nodal basin recurrence in patients who had only a pelvic LND performed at the time of their initial staging surgery, compared to those who had both a pelvic and paraaortic LND. More patients undergoing both a pelvic and paraaortic LND received adjuvant chemotherapy (160 vs. 84, $p<0.0001$); however, in this subgroup receiving chemotherapy, patients who underwent only a pelvic LND still had more paraaortic nodal basin recurrences (8 vs. 2, $p=0.0036$) [16]. Our data does not support the routine removal of benign-appearing paraaortic lymph nodes. We did not demonstrate a difference in OS or PFS between the two cohorts, after adjusting for stage and adjuvant therapy, and presence of positive paraaortic nodes was not associated with poorer OS. With increasing use of combination chemotherapy and radiation for stage IIIC1 disease, the identification of additional metastatic paraaortic nodes may not influence outcome. There is still the possibility of missing isolated paraaortic lymph node metastases (i.e. positive paraaortic lymph nodes in a patient with negative pelvic lymph nodes). Our data does not assess the percentage of isolated paraaortic lymph node metastases present in either cohort; however the rate in intermediate and high-risk patients is very low [13]. In a study that did not include SLN assessment, Kim et al demonstrated that the rate of isolated paraaortic lymph node metastases decreased as an increasing number of pelvic lymph nodes were removed, suggesting that the rate of truly isolated paraaortic lymph node metastases is low; detection depends mainly on accurate identification of the positive pelvic node [17]. This

suggests that the rate may be lower in SLN cases when the positive pelvic lymph nodes are more frequently identified [5, 18].

Concern has also been expressed regarding the potential consequences of false negative sentinel nodes. The false negative rate of the SLN algorithm used in this study has previously been reported as 1.9% [7]. Similarly, the investigators of the SENTI-ENDO trial, a large, prospective study of the use of an SLN algorithm in endometrial carcinoma, demonstrated a false negative rate of 2.4%; all of the false negative cases were in patients with non-endometrioid histology [11]. Naoura et al reported an increased risk of false negative SLNs in patients with high-risk disease as defined by the European Society for Medical Oncology (ESMO) [19]; this included grade 3 deeply invasive EECs, as well as all non-endometrioid adenocarcinomas [20]. Naoura and colleagues reported that 6 of the identified 9 false negative cases had unilateral mapping, emphasizing the importance of a side-specific full LND in a non-mapping hemipelvis [20]. Though we did not assess the false negative rate directly, we demonstrate similar OS and PFS between the two cohorts, specifically in patients with negative lymph nodes. As well, there appears to be no difference in the rate of lymphatic recurrences--used by some as a surrogate for false negative lymph nodes--between the SLN and LND cohorts. These data, in this small subgroup, are reassuring and indicate that, when using an SLN algorithm in the setting of deeply invasive EEC, the risk of missing metastatic lymph nodes is low.

The therapeutic role of lymphadenectomy has not yet been proven in a prospective, randomized trial. Holloway et al found that in a group of 119 patients who underwent SLN mapping followed by full pelvic LND with or without paraaortic LND, based on uterine features, 48.6% of the 35 cases with a positive SLN also had metastatic non-sentinel nodes [18]. Mariani et al found improved 5-year PFS (76.1% vs 36.1%, $p=0.02$) and OS (76.9% vs 42%, $p=0.053$) in a group of patients with EEC and positive lymph nodes who underwent paraaortic LND ($n=13$) compared to those who did not ($n=38$), suggesting a therapeutic benefit to more extensive LND in patients with positive pelvic lymph nodes [21]. Though extensively criticized, two large randomized trials did not demonstrate an advantage to LND with respect to OS. However, these trials included minimally invasive and non-endometrioid disease, limiting our ability to draw conclusions about the patient population in our study [22, 23]. In this study, we did not include stage IIIC patients with widespread grossly enlarged metastatic lymph nodes, which are not treated with the SLN approach. For this reason, we cannot comment on the possible number of non-resected metastatic lymph nodes in either of the cohorts. However, despite significant differences in the number of both pelvic and paraaortic lymph nodes removed, we did not demonstrate any difference in PFS or OS. As patients with stage IIIC1 disease are likely to receive adjuvant combined chemotherapy and radiation therapy, it is unclear whether additional removal of benign-appearing lymph nodes is worth the attendant intraoperative and long-term risks of a more extensive LND.

The two cohorts in our study differed with regards to adjuvant therapy, despite similar stage distribution. This was also true of the subgroup with negative or unassessed lymph nodes, where the majority of patients in both cohorts had stage I disease. On multivariable analysis in the overall cohort, adjuvant therapy--in particular, adjuvant chemotherapy combined with external beam radiation (EBRT) with or without brachytherapy--was a significant predictor

of OS on multivariable analysis in the overall cohort. However, adjuvant therapy was no longer associated with OS in the subgroup of patients with negative or unassessed lymph nodes. Adjuvant therapy was found to be a confounding factor in the study population as a whole. In our analysis, we controlled for the effect of adjuvant therapy on survival, and no difference in outcomes was seen between the two cohorts. Further evaluation of the effect of adjuvant therapy on outcomes is not possible within the parameters of the retrospective cohort design.

The recently published results from PORTEC-3 demonstrated no difference in OS between high-risk endometrial cancer patients receiving adjuvant radiation alone versus chemotherapy with radiation; however, the addition of chemotherapy did improve failure-free survival, particularly in patients with stage III disease [24]. This highlights the importance of surgical staging in endometrial cancer to help guide adjuvant treatment recommendations. The preliminary results of GOG-258, a study comparing chemotherapy to chemotherapy with radiation in advanced stage endometrial cancer, demonstrate no difference in recurrence-free survival [25]. (The OS data is immature and has not yet been published. Our data corroborates the PORTEC-3 data, suggesting that adjuvant chemotherapy is not beneficial in early stage, high-risk endometrial cancer. We await the publication of the GOG-258 final results, which should provide guidance on appropriate adjuvant therapy in patients with advanced disease.

The major strength of our study is the comparison of two large groups of patients with deeply invasive EEC from two institutions with surgical staging paradigms that differed only in the method of lymph node assessment. The involvement of two institutions did limit the ability to standardize or control a variety of potential confounding factors. There were differences in pathologic interpretation between the two cohorts, as well as significant differences in the administration of adjuvant therapy. LVSI was more frequently identified in the SLN cohort, which may have contributed to the increased administration of adjuvant therapy in that cohort. This difference in adjuvant treatment may also have affected OS and PFS. Our study may also have been limited by size. Given the sample size and number of deaths within the first 3 years following surgery, our study had 80% power to detect a hazard ratio of 3.10 or higher.

Our study did not address the perioperative or long-term adverse effects of either intervention. Emerging data indicates that there is decreased lymphedema with the use of an SLN algorithm. In a retrospective cohort of endometrial cancer patients, Geppert et al demonstrated a leg lymphedema rate of 1.3% with SLN biopsy alone, compared to 18.1% with full pelvic and paraaortic LND [26]. Leitaio et al surveyed 623 patients who underwent hysterectomy alone, hysterectomy with SLN assessment, or hysterectomy with full LND, and found that after controlling for BMI and receipt of adjuvant EBRT, full LND retained an independent association with lower extremity lymphedema, compared to SLN assessment (OR 1.8; 95% CI 1.22-2.69) [27]. Long-term complications of surgical interventions should be considered when evaluating innovative surgical techniques, and more data evaluating the rates of lymphedema associated with utilization of an SLN algorithm are needed.

We also did not assess the morbidity associated with the treatment plan as a whole, including adjuvant therapy. More patients in the SLN cohort received adjuvant therapy, compared to the LND cohort. While emerging data suggests decreased surgical morbidity with an SLN algorithm, it is unclear if the added morbidity of additional treatment negates this benefit. Additional evaluation is needed to determine the best overall treatment plan for surgically staged women with deeply invasive EEC.

In conclusion, oncologic outcomes are not impaired with the use of a SLN algorithm, compared to full pelvic and paraaortic LND, in patients with deeply invasive EEC. When determining optimal interventions for endometrial cancer patients, it is important to balance the risks of treatment-related adverse effects with effects on oncologic outcomes. Many unanswered questions remain regarding the management of high-risk patients. Future studies should evaluate the role of adjuvant combined chemotherapy and radiation, particularly in node negative patients; the use of an SLN algorithm in non-endometrioid histologies; and the rate of symptomatic lymphedema following SLN dissection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- SLN assessment does not adversely affect outcomes in deeply invasive endometrioid endometrial cancer.
- Survival is excellent in node-negative cases regardless of nodal assessment method.
- Nodal recurrence rates are similar between SLN and full LND.

Figure 1. Sentinel lymph node mapping and additional lymphadenectomy details of the SLN cohort. SLN = sentinel lymph node, LND = lymphadenectomy

Table 1:

Clinical and pathologic characteristics

Characteristic	SLN Cohort (N=82)	LND Cohort (N=94)	P [†]
Age (years), mean (SD)	64.3 (±10.2)	69.2 (±10.92)	0.003
BMI (kg/m ²), mean (SD)	29.8 (±6.8)	31.6 (±8.1)	0.10
FIGO grade, N (%)			0.44
1	29 (35.4)	34 (36.2)	
2	31 (37.8)	42 (44.7)	
3	22 (26.8)	18 (19.1)	
FIGO stage (2009), N (%)			0.16
I	46 (56.1)	60 (63.8)	
II	5 (6.1)	10 (10.6)	
III	31 (37.8)	24 (25.5)	
LVSI, N (%)	61 (74.4)	29 (30.9)	<0.001
Cervical stromal invasion, N (%)	11 (13.4)	15 (16.0)	0.64
Malignant peritoneal cytology, N (%)	12 (14.6)	18/88 (20.5) [‡]	0.32
Adjuvant therapy, N (%)			<0.001
None	8 (9.8)	28 (29.8)	
IVRT	30 (36.6)	18 (19.1)	
EBRT ± IVRT	7 (8.5)	4 (4.3)	
Chemotherapy ± IVRT	16 (19.5)	18 (19.1)	
Chemotherapy and EBRT ± IVRT	21 (25.6)	13 (13.8)	
Unknown	0 (0)	13 (13.8)	

BMI=body mass index, EBRT=external beam radiation therapy, FIGO=International Federation of Gynecology and Obstetrics, IVRT=intravaginal brachytherapy, LVSI=lymphovascular space invasion, SD=standard deviation

[†] Comparisons between groups were evaluated using the Two-sample T-test for age and BMI, and the Chi-square test for all other categorical baseline characteristics.

[‡] Six patients with unknown peritoneal cytology sampling were omitted from the univariate analysis.

Table 2:

Lymphadenectomy characteristics

Lymphadenectomy Characteristic	SLN Cohort (N=82)	LND Cohort (N=94)	P [†]
Pelvic LN assessment, N (%)			0.12
Yes	81 (98.8)	88 (93.6)	
No	1 (1.2)	6 (6.4)	
Number of pelvic nodes removed, median (IQR) *	10 (4, 14)	34 (27, 44)	<0.001
Positive pelvic lymph nodes, N (%)			0.003
Yes	27 (32.9%)	13 (13.8)	
No or pelvic LND not performed	55 (67.1%)	81 (86.2)	
Positive pelvic lymph nodes, N (%) *			0.005
Yes	27 (33.3%)	13 (14.8)	
No	54 (66.7%)	75 (85.2)	
Para-aortic LND, N (%)			<0.001
Yes	28 (34.1%)	85 (90.4)	
No or para-aortic LND not performed	54 (65.9%)	9 (9.6)	
Number of para-aortic nodes removed, median (IQR) *	5 (2, 9)	17 (12, 22)	<0.001
Positive para-aortic nodes, N (%)			0.01
Yes	3 (3.7)	14 (14.9)	
No or para-aortic LND not performed	79 (96.3)	80 (85.1)	
Positive para-aortic nodes, N (%) *			0.56
Yes	3 (10.7)	14 (16.5)	
No	25 (89.3)	71 (83.5)	

IQR=interquartile range, LND=lymphadenectomy

* Limited to patients with specified lymphadenectomy

† Comparisons between groups were evaluated using the Chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for number of nodes.

Table 3:

Comparison of outcomes of the 2 different surgical approaches within the first three years following surgery for the entire cohort, and the subset with negative lymph nodes or without lymphadenectomy performed, respectively

Outcome	No. of events within 3 years	Unadjusted 3-year Kaplan-Meier rates (%) (95% CI)		HR for LND vs. SLN (95% CI)		
		SLN	LND	Unadjusted	Adjusted for age [†]	Adjusted for age and adjuvant therapy
Entire cohort						
PFS	32	78.7 (69.6, 89.1)	77.7 (68.6, 87.9)	0.96 (0.48, 1.93)	0.86 (0.40, 1.86)	0.87 (0.40, 1.89) [‡]
Non-vaginal PFS	23	83.0 (74.5, 92.4)	84.6 (76.3, 93.8)	0.79 (0.35, 1.78)	0.70 (0.28, 1.75)	0.77 (0.30, 1.96) [‡]
OS	24	91.8 (85.0, 99.1)	77.6 (69.0, 87.2)	3.23 (1.21, 8.65)	2.45 (0.83, 7.28)	2.54 (0.81, 7.91) [‡]
Subset with negative lymph nodes or no LND performed						
PFS	22	74.7 (62.7, 89.1)	81.3 (71.7, 92.3)	0.64 (0.28, 1.48)	0.69 (0.26, 1.83)	0.69 (0.23, 2.03) [^]
Non-vaginal PFS	16	79.4 (68.2, 92.6)	87.1 (78.3, 96.9)	0.50 (0.19, 1.35)	0.52 (0.16, 1.65)	0.67 (0.19, 2.33) [^]
OS	14	91.9 (83.4, 100.0)	83.2 (74.5, 93.0)	2.46 (0.69, 8.83)	1.03 (0.23, 4.67)	0.81 (0.16, 4.22) [^]

CI=confidence interval, EBRT=external beam radiation therapy, IVRT=intravaginal brachytherapy, LND=lymphadenectomy, OS=overall survival, PFS=progression-free survival, SLN=sentinel lymph node

[†] Cox regression model fit using age as the time scale (instead of time since surgery) in order to adjust for age, given the difference in age at surgery between the two cohorts

[‡] Cox regression model fit using age as the time scale and including a 3-level covariate to adjust for adjuvant therapy (none/unknown/IVRT vs. EBRT ± IVRT vs. Chemotherapy ± EBRT ± IVRT)

[^] Cox regression model fit using age as the time scale and including a 2-level covariate to adjust for adjuvant therapy (none/unknown vs. any therapy).

Table 4:

Univariate analysis of factors associated with overall survival based on all 176 patients

Characteristic	Univariate analysis [†]	
	HR (95% CI)	P
Age (years) [‡]	1.76 (1.14, 2.72)	0.01
BMI (kg/m ²) [‡]	0.88 (0.66, 1.16)	0.36
FIGO grade		0.009
1	Reference	
2	2.22 (0.70, 7.10)	
3	5.66 (1.76, 18.24)	
FIGO stage (2009)		0.001
I	Reference	
II	1.65 (0.35, 7.77)	
III	5.00 (2.07, 12.10)	
LVSI		0.005
No	Reference	
Yes	3.51 (1.46, 8.46)	
Cervical stromal invasion		0.008
No	Reference	
Yes	3.18 (1.36, 7.45)	
Malignant peritoneal cytology		0.001
No or not assessed	Reference	
Yes	3.87 (1.71, 8.75)	
Presence of positive paraaortic nodes		0.17
No or paraaortic LND not performed	Reference	
Yes	2.00 (0.74, 5.45)	
Adjuvant therapy		0.26
None or unknown or IVRT only	Reference	
EBRT ± IVRT	1.29 (0.29, 5.71)	
Chemotherapy ± EBRT ± IVRT	0.46 (0.17, 1.25)	

BMI=body mass index, CI=confidence interval, EBRT=external beam radiation therapy, FIGO=International Federation of Gynecology and Obstetrics, HR=hazard ratio, IVRT=intravaginal brachytherapy, LND=lymphadenectomy, LVSI=lymphovascular space invasion, OS=overall survival, SLN=sentinel lymph node

[†] Each factor was evaluated in a separate univariate stratified Cox proportional hazards regression model, stratified by cohort (SLN vs. LND), to accommodate a separate hazard function for each cohort given the different patient populations.

[‡] Hazard ratio per 10-year increase in age and per 5-unit increase in BMI

Table 5:

Clinical and pathologic characteristics of patients with either negative lymph nodes or no lymphadenectomy performed

Characteristic	SLN Cohort (N=53)	LND Cohort (N=74)	P [†]
Age (years), mean (SD)	64.0 (±10.2)	69.4 (±10.6)	0.005
BMI (kg/m ²), mean (SD)	29.5 (±7.1)	31.7 (±8.2)	0.12
FIGO grade, N (%)			0.06
1	13 (24.5)	30 (40.5)	
2	23 (43.4)	32 (43.2)	
3	17 (32.1)	12 (16.2)	
FIGO stage (2009), N (%)			0.70
I	46 (86.8)	60 (81.1)	
II	5 (9.4)	10 (13.5)	
III	2 (3.8)	4 (5.4)	
LVSI, N (%)	33 (62.3)	20 (27.0)	<0.001
Cervical stromal invasion, N (%)	5 (9.4)	12 (16.2)	0.27
Malignant peritoneal cytology, N (%)	5 (9.4)	12/69 (17.4) [‡]	0.21
Pelvic LND performed, N (%)	52 (98.1)	68 (91.9)	0.24
Para-aortic LND performed, N (%)	17 (32.1)	65 (87.8)	<0.001
Adjuvant therapy, N (%)			<0.001
None	6 (11.3)	25 (33.8)	
IVRT	29 (54.7)	18 (24.3)	
EBRT ± IVRT	6 (11.3)	1 (1.4)	
Chemotherapy ± IVRT	9 (17.0)	15 (20.3)	
Chemotherapy and EBRT ± IVRT	3 (5.7)	4 (5.4)	
Unknown	0 (0)	11 (14.9)	

BMI=body mass index, EBRT=external beam radiation therapy, FIGO=International Federation of Gynecology and Obstetrics, IVRT=intravaginal brachytherapy, LND= lymphadenectomy, LVSI=lymphovascular space invasion, SD=standard deviation

[†]Comparisons between groups were evaluated using the two-sample t-test for age and BMI, and the chi-square test for all other categorical baseline characteristics.

[‡]Five patients with unknown peritoneal cytology sampling were omitted from the univariate analysis.

Univariate analysis of factors associated with progression-free survival and overall survival in patients with negative lymph nodes or without lymphadenectomy performed

Table 6:

Characteristic	PFS		Non-vaginal PFS		OS	
	HR (95% CI) [‡]	P	HR (95% CI) [‡]	P	HR (95% CI) [‡]	P
Age (years) [‡]	1.16 (0.75, 1.79)	0.50	1.01 (0.62, 1.65)	0.97	2.53 (1.35, 4.73)	0.004
BMI (kg/m ²) [‡]	0.86 (0.63, 1.16)	0.32	0.77 (0.52, 1.13)	0.18	0.77 (0.51, 1.15)	0.19
FIGO grade	Reference	0.18	Reference	0.24	Reference	0.35
1						
2	2.48 (0.79, 7.85)		2.09 (0.54, 8.13)		2.21 (0.57, 8.58)	
3	3.17 (0.89, 11.27)		3.43 (0.82, 14.40)		2.99 (0.65, 13.73)	
FIGO stage (2009)		0.19		0.03		<0.001
I	Reference		Reference		Reference	
II	2.53 (0.92, 6.92)		4.09 (1.39, 12.02)		1.68 (0.36, 7.95)	
III	1.76 (0.23, 13.63)		2.63 (0.33, 21.17)		12.70 (3.63, 44.46)	
LVSI		0.08		0.31		0.02
No	Reference		Reference		Reference	
Yes	2.24 (0.90, 5.60)		1.75 (0.60, 5.08)		3.75 (1.22, 11.54)	
Cervical stromal invasion		0.02		0.002		0.11
No	Reference		Reference		Reference	
Yes	3.03 (1.18, 7.81)		4.96 (1.79, 13.76)		2.57 (0.80, 8.22)	
Malignant peritoneal cytology		0.58		0.24		0.02
No or not assessed	Reference		Reference		Reference	
Yes	1.42 (0.42, 4.84)		2.12 (0.60, 7.54)		3.94 (1.31, 11.91)	
Adjuvant therapy		0.50		0.11		0.57
None or unknown or IVRT only	Reference		Reference		Reference	
EBRT ± IVRT	2.23 (0.47, 10.70)		3.63 (0.69, 19.09)		1.63 (0.18, 14.97)	
Chemotherapy ± EBRT ± IVRT	1.46 (0.58, 3.67)		2.70 (0.95, 7.71)		0.49 (0.11, 2.22)	

BMI=body mass index, CI=confidence interval, EBRT=external beam radiation therapy, FIGO=International Federation of Gynecology and Obstetrics, HR=hazard ratio, IVRT=intravaginal brachytherapy, LND=lymphadenectomy, LVSI=lymphovascular space invasion, OS=overall survival, PFS=progression-free survival, SLN=sentinel lymph node

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Each factor was evaluated in a separate univariate stratified Cox proportional hazards regression model, stratified by cohort (SLN vs. LND), to accommodate a separate hazard function for each cohort given the different patient populations.

Hazard ratio per 10-year increase in age and per 5-unit increase in BMI.