# Impact of comorbidities and extent of lymphadenectomy on quality of life in endometrial cancer patients treated with minimally invasive surgery in the era of sentinel lymph nodes

Giorgia Dinoi,[1] Francesco Multinu ,[2] Kathleen Yost,[3] Mariam AlHilli,[4] Alyssa Larish,[5] Carrie Langstraat ,[5] Amanika Kumar ,[5] Amy L Weaver,[6] Michaela McGree,[6] Andrea Cheville,[7] Sean Dowdy,[5] Andrea Mariani ,[5] Gretchen Glaser [5]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2023-004423).

For numbered affiliations see end of article.

**Correspondence to**
Dr Gretchen Glaser, Mayo Clinic, Rochester, MN 55905, USA; glaser.gretchen@mayo.edu

Received 27 February 2023
Accepted 21 June 2023
Published Online First 6 July 2023



**To cite:** Dinoi G, Multinu F, Yost K, *et al. Int J Gynecol Cancer* 2023;**33**:1227–1236.

## ABSTRACT

**Objective** To identify predictors of quality of life (QoL) among patients who undergo surgical staging with sentinel lymph node (SLN) biopsy or lymphadenectomy for endometrial cancer.

**Methods** Patients who underwent minimally invasive surgery for primary endometrial cancer at the Mayo Clinic from October 2013 to June 2016 were mailed a 30-item QoL in Cancer survey (QLQ-C30) and a validated 13-item lower extremity lymphedema screening questionnaire. Patients who answered <50% of the items or had a pre-operative history of lymphedema were excluded. Multivariable linear regression models were fit to evaluate predictors of QoL using inverse-probability of treatment weighting to adjust for differences at the time of the surgery between the lymphadenectomy and SLN groups.

**Results** The 221 patients included in the analysis were stratified into two groups: patients who underwent (1) bilateral lymphadenectomy as 'backup' after SLN mapping (lymphadenectomy group; n=101) or (2) SLN removal with or without side-specific lymphadenectomy (SLN group; n=120). On multivariable analysis, obesity, lower extremity lymphedema, and kidney disease had significant ($p<0.05$) and clinically meaningful negative impacts on global QoL. Declines in average adjusted global QoL scores were marked (19.7 points lower) in patients with BMI ≥40 kg/m$^2$ and lower extremity lymphedema compared with non-obese patients without lower extremity lymphedema. In contrast, there was only a 2.9 point difference in the adjusted average global QoL score between the SLN and lymphadenectomy groups.

**Conclusions** Lower extremity lymphedema coupled with obesity predicts poorer QoL in patients who undergo surgical staging for endometrial cancer. In this population, reduction of lower extremity lymphedema by performing SLN instead of lymphadenectomy and earlier targeted interventions may improve patients' QoL. Future research focusing on targeted interventions is needed.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Investigations on quality of life (QoL) in patients undergoing surgery with sentinel lymph node biopsy are lacking in the literature. As women with endometrial cancer are likely to have long-term survival after their disease, an urgency exists for enhancing our understanding.

### WHAT THIS STUDY ADDS

⇒ This comparison of QoL among endometrial cancer patients who undergo sentinel lymph node biopsy versus lymphadenectomy shows that lower extremity lymphedema coupled with obesity strongly predicts poorer QoL in patients with endometrial cancer who undergo surgical staging.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our work provides intriguing data from which prospective assessments and targeted interventions to improve QoL in patients with endometrial cancer can be designed. This will help improve QoL during long-term survivorship for patients with the most common gynecologic malignancy.

## INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy.[1] Most endometrial cancers are diagnosed when the disease is still confined to the uterus; thus approximately 80% of patients are alive 5 years after diagnosis.[2–4] The most common treatment for endometrial cancer includes surgical staging (hysterectomy with lymph node assessment) with or without adjuvant therapy.[5] These treatments increase the risk for lower extremity lymphedema with attendant decreases in quality of life (QoL).[6 7] The LymphEdema and Gynecologic Cancer Study reported similar findings of lower extremity lymphedema after lymphadenectomy for gynecologic cancers including endometrial, cervical, and vulvar,[8] as well as confirmed measurable changes in QoL ($p<0.001$).[9 10] Lower extremity lymphedema is defined as a change in bioimpedance or limb volume compared with the opposite leg, and

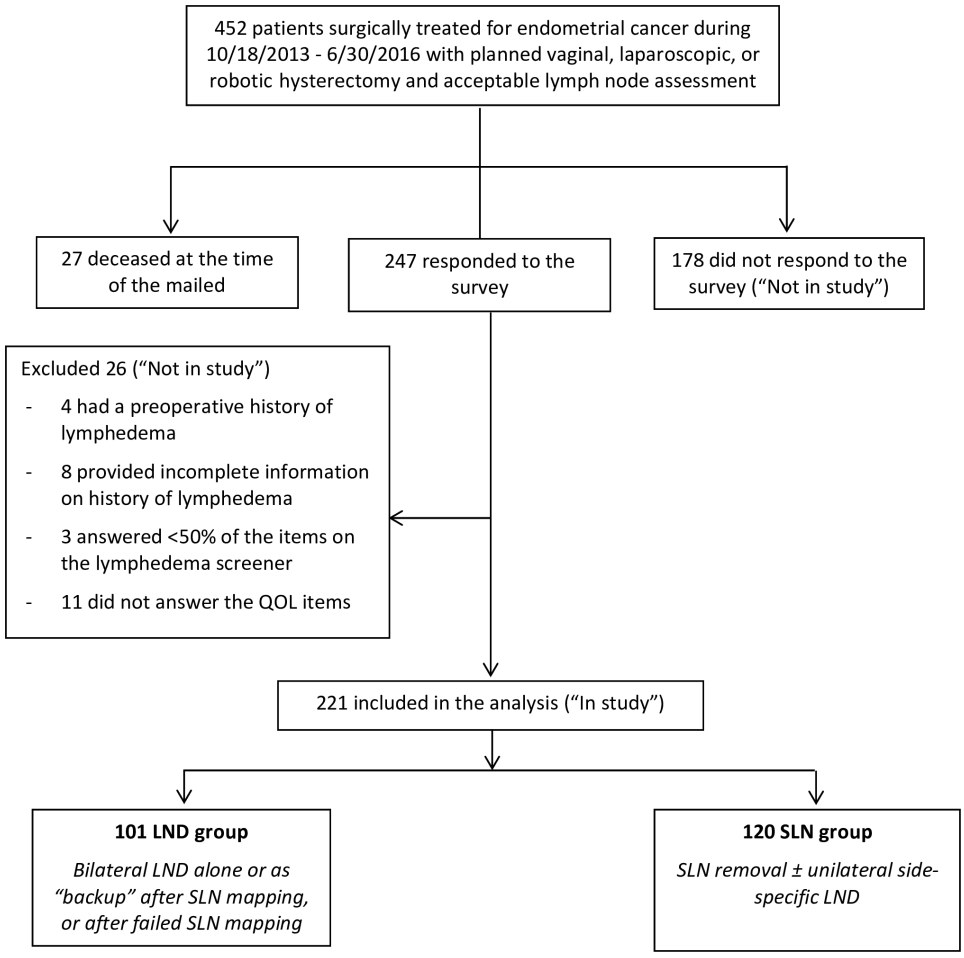


**Figure 1** Flow diagram of included patients. LND, lymphadenectomy; QOL, quality of life; SLN, sentinel lymph node.

may be associated with discomfort, disfigurement, and decreased mobility, as well as difficulty diagnosing with current techniques.[11]

National Comprehensive Cancer Center Network (NCCN) guidelines now include sentinel lymph node (SLN) biopsy as the preferred option for surgical staging of endometrial cancer.[5 12–14] In an analysis of patients undergoing surgery for endometrial cancer before and after the implementation of SLN biopsy, we demonstrated that SLN biopsy was associated with significantly less lower extremity lymphedema than lymphadenectomy (26% vs 49%, p<0.001).[15 16]

Our objective in this study was to identify predictors of quality of life (QoL) among patients who undergo surgical staging with SLN biopsy or lymphadenectomy for endometrial cancer. We hypothesized that patients who were staged with SLN biopsy would have significantly better QoL than those who underwent lymphadenectomy.

## METHODS

This study was approved by the Mayo Clinic Institutional Review Board (09-0 04 517). Patients who underwent surgery for newly diagnosed endometrial cancer at the Mayo Clinic in Rochester, Minnesota, between October 18, 2013 and June 30, 2016, provided research authorization, did not have synchronous cancer, and did not receive neoadjuvant therapy were included. SLN biopsy was performed for endometrial cancer staging (all histologies) at our institution starting on October 18, 2013. Patients with a planned open, laparoscopic, or robotic lymph node assessment were included in this analysis. Patients who had a pre-operative history of lymphedema or provided incomplete information on history of lymphedema, who answered <50% of the items on the lymphedema screener, or did not answer the QoL items were excluded. All patients underwent hysterectomy with or without bilateral salpingo-oophorectomy. Indocyanine green was used for the majority of SLN identification (70.1%).[17] Early in the transition to SLN biopsy, we used blue dye for this procedure.

Two groups were identified based on the intended mode of staging for endometrial cancer: (1) a group who underwent bilateral lymphadenectomy without attempting SLN mapping or as 'backup' after SLN mapping during our period of transition to SLN biopsy; and (2) a group who underwent SLN removal only or SLN removal and side-specific lymphadenectomy for no mapping per the NCCN algorithm.[5 12 15]

Patients were mailed a survey that included queries for a self-reported history of clinically-diagnosed lower extremity lymphedema, comorbidities known to be associated with lower extremity lymphedema, a 13-item validated patient-reported outcome screening questionnaire (lymphedema screener) assessing symptoms in the past 4 weeks, and the 30-question Quality of Life in Cancer instrument (QLQ-C30).[6 7 18] If no response was received after 1 month, a second survey was mailed. In patients who did

**Table 1** Characteristics of minimally invasive surgery patients in study, not in study, and those deceased

| Characteristic | In study n=221 | Not in study n=204 | Deceased at time of mailing n=27 | P* |
|---|---|---|---|---|
| At the time of the surgery | | | | |
| Age (years), mean (SD) | 64.7 (8.9) | 63.7 (10.4) | 72.8 (11.5) | 0.27 |
| BMI (kg/m$^2$), median (IQR) | 32.9 (27.6–38.6) | 34.7 (27.9–41.2) | 29.3 (27.5–38.6) | 0.05 |
| BMI (kg/m$^2$), N (%) | | | | 0.04 |
| <25.0 | 29 (13.1) | 28 (13.7) | 4 (14.8) | |
| 25.0–29.9 | 54 (24.4) | 35 (17.2) | 10 (37.0) | |
| 30.0–39.9 | 95 (43.0) | 79 (38.7) | 10 (37.0) | |
| 40.0 or higher | 43 (19.5) | 62 (30.4) | 3 (11.1) | |
| ASA score, N (%) | | | | 0.01 |
| <3 | 171 (77.4) | 136 (66.7) | 14 (51.9) | |
| ≥3 | 50 (22.6) | 68 (33.3) | 13 (48.1) | |
| Comorbidities, N (%) | | | | |
| Diabetes | 31 (14.0) | 35 (17.2) | 5 (18.5) | 0.37 |
| Chronic heart failure | 6 (2.7) | 2 (1.0) | 3 (11.1) | 0.29 |
| Moderate/severe renal disease | 4 (1.8) | 6 (2.9) | 2 (7.4) | 0.53 |
| Surgical details | | | | |
| FIGO grade, N (%) | | | | 0.89 |
| 1 | 111 (50.2) | 99 (48.5) | 4 (14.8) | |
| 2 | 51 (23.1) | 51 (25.0) | 5 (18.5) | |
| 3 | 59 (26.7) | 54 (26.5) | 18 (66.7) | |
| FIGO stage, N (%) | | | | 0.36 |
| I/II | 202 (91.4) | 181 (88.7) | 11 (40.7) | |
| III/IV | 19 (8.6) | 23 (11.3) | 16 (59.3) | |
| Histology, N (%)† | | | | 0.62 |
| Non-endometrioid | 35 (15.8) | 36 (17.6) | 13 (48.1) | |
| Endometrioid | 186 (84.2) | 168 (82.4) | 14 (51.9) | |
| Study group, N (%) | | | | 0.74 |
| LND | 101 (45.7) | 90 (44.1) | 13 (48.1) | |
| SLN | 120 (54.3) | 114 (55.9) | 14 (51.9) | |
| Total nodes removed via SLN among those with nodes removed, median (IQR) | 3 (2–4) | 3 (2–4) | 3 (1–3) | 0.85 |
| LND performed, N (%) | | | | 0.21 |
| No | 103 (46.6) | 91 (44.6) | 13 (48.1) | |
| Pelvic only | 69 (31.2) | 74 (36.3) | 4 (14.8) | |
| Para-aortic only | 2 (0.9) | 6 (2.9) | – | |
| Pelvic and para-aortic | 47 (21.3) | 33 (16.2) | 10 (37.0) | |
| Total nodes removed via LND among those with nodes removed, median (IQR) | | | | |
| Total pelvic and para-aortic | 24 (16–31) | 21 (14–32) | 22 (18–24) | 0.34 |
| Total pelvic | 20 (15–26) | 20 (14–26) | 14 (10–20) | 0.83 |
| Total para-aortic | 10 (7–18) | 10 (6–16) | 9 (3–10) | 0.70 |
| Total nodes removed by any means (SLN+LND), median (IQR) | 9 (4–26) | 9 (3–24) | 6 (3–22) | 0.80 |
| Adjuvant therapy, N (%) | | | | 0.02 |
| None or VB alone | 184 (83.3) | 160 (78.4) | 11 (40.7) | |
| EBRT±VB | 3 (1.4) | 1 (0.5) | 2 (7.4) | |
| Chemotherapy±VB | 21 (9.5) | 13 (6.4) | 5 (18.5) | |

Continued

**Table 1** Continued

| Characteristic | In study n=221 | Not in study n=204 | Deceased at time of mailing n=27 | P* |
|---|---|---|---|---|
| Chemotherapy and EBRT±VB | 8 (3.6) | 13 (6.4) | 5 (18.5) | |
| Unknown | 5 (2.3) | 17 (8.3) | 4 (14.8) | |

*Comparison between 'In study' and 'Not in study' only; comparisons were evaluated using the two-sample t-test for age, Wilcoxon rank-sum test for all other continuous or ordinal variables, and $\chi^2$ or Fisher's exact for categorical variables. P<0.05 was considered statistically significant.
†Endometrioid histology includes endometrioid and mixed endometrioid and mucinous histology; non-endometrioid histology includes serous, clear cell, carcinosarcoma, undifferentiated, mixed serous, mixed clear cell, and mixed undifferentiated histology.
ASA, American Society of Anesthesiologists; BMI, body mass index; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range (25th and 75th percentiles); LND, lymphadenectomy; SLN, sentinel lymph node sampling; VB, vaginal brachytherapy.

not respond to the second survey, contact was initiated by phone. Two data specialists from the Mayo Clinic Survey Research Center independently entered survey responses obtained by email or by phone. Discrepancies between data specialists were reconciled against the survey.

The surveys were chosen for their pertinence in assessing both QoL and lymphedema in our population. In the lymphedema screener questionnaire each question was scored from 0 (not at all) to 4 (very much), with a score of 5 or higher identifying women with lower extremity lymphedema. The QLQ-C30 shows sensitivity values between 0.71 and 0.97 and specificity values between 0.62 and 0.92 (area under the curve >0.80 for all scales) for generated thresholds of clinical importance.[19] The lymphedema screener's sensitivity and specificity for detecting lower extremity lymphedema is 95.5% and 86.5% respectively overall, and 94.8% and 76.5% respectively in obese patients.

Using the items from the QLQ-C30, nine functional and symptom scales were scored on a scale from 0 to 100 following the recommended scoring procedures; a scale score was not calculated if more than half of the items contributing to that score were missing. Lower extremity lymphedema was defined using self-reported diagnosis made by a health professional after surgery or a 'screen positive' on the lymphedema screener.[6]

Data abstracted from medical records included clinical, surgical and pathological details, and receipt of adjuvant external beam radiation therapy±chemotherapy. The following were self-reported by the patient at the time of the survey: body mass index (BMI), comorbidities (diabetes, chronic heart failure, and moderate/severe renal disease), receipt of external beam radiation therapy after surgery, and diagnosis of recurrence.

### Data Analysis

Data management and analysis were conducted using the SAS version 9.4 software package. Data were summarized using standard descriptive statistics; frequencies and percentages for categorical variables and mean and SD or median and IQR for continuous variables. To assess participation bias and generalizability of our results, we summarized the baseline patient characteristics of survey respondents ('In study'), deceased patients, and non-respondents or those subsequently excluded ('Not in study'). Comparisons of baseline characteristics between the 'In study' and 'Not in study' groups were evaluated using the $\chi^2$ or Fisher's exact test for categorical variables, the two-sample t-test for age, and the Wilcoxon rank-sum test for all other continuously scaled variables. In addition, these same baseline characteristics along with characteristics at the time of the survey were compared between two 'In study' groups (lymphadenectomy vs SLN) using the forementioned statistical methods.

Given the retrospective nature of these data and that patients were not randomly assigned to the type of staging (lymphadenectomy vs SLN), propensity score methodology with inverse-probability of treatment weighting was used to derive an adjusted cohort in which the lymphadenectomy and SLN groups were more balanced on measured baseline covariates (see description in online supplemental table 1). Each QoL scale was compared between the lymphadenectomy and SLN groups using the Wilcoxon rank sum test in the unadjusted cohort and by fitting a simple linear regression model separately in the unadjusted cohort and the adjusted cohort. In addition, using the adjusted cohort, for each QoL scale, a multivariable linear regression model was fit to evaluate the impact of type of staging, lower extremity lymphedema, and obesity on the QoL score, adjusting for age, having ever received external beam radiation therapy after the hysterectomy, and comorbidities at the time of the survey. Given the known relationship between lower extremity lymphedema and obesity, we created indicator variables to evaluate the additive effect of one or both of these factors. A difference of ≥10 points on each 0–100 point QoL scale was considered as clinically meaningful.[20] All calculated p values were two-sided and p values <0.05 were considered statistically significant.

The propensity score values, defined as the estimated probability of meeting criteria for the lymphadenectomy group (vs the SLN group), were derived from a multivariable logistic regression model (with lymphadenectomy vs SLN as the binary dependent variable) that included the covariates listed in online supplemental table 2. These covariates were pre-selected based on available factors in our cohort previously known to be risk factors for poor outcomes or observed to be different between the lymphadenectomy and SLN groups.[21] Weights were derived and evaluated using the process described in online supplemental table 1.

## RESULTS

Of 452 patients who underwent minimally invasive surgery with surgical staging during the study period that met the inclusion criteria, 27 were deceased at the time of the survey mailing, 178 did not return a survey, 26 returned a survey but met additional exclusion criteria, and 221 returned a survey and were included in the analysis, as summarized in the flowchart (figure 1). Characteristics

of patients 'In study', 'Not in study', and 'Deceased at the time of mailing' are presented in table 1. The 'In study' versus 'Not in study' groups were statistically compared; the median BMI was significantly lower for 'In study' patients (median 32.9 vs 34.7 kg/m$^2$, p=0.05) and these patients were more likely to have an American Society of Anesthesiologists (ASA) score <3 (77.4% vs 66.7%, p=0.01).

Among the 221 'In study' patients, 101 met criteria for the lymphadenectomy group and 120 for the SLN group. Patient characteristics at the time of surgery and at the time of the survey for each group are summarized in table 2. The median BMI was significantly lower in the lymphadenectomy group, both at the time of the surgery and at the time of the survey (p=0.019 and p=0.04, respectively), with differences in medians of 1.4 and 1.5, respectively. Comorbidities such as diabetes, chronic heart failure, and moderate/severe renal disease were rare. We found no statistically significant difference in International Federation of Gynecology and Obstetrics (FIGO) staging, but there was a statistically significant difference in FIGO grading; patients in the lymph node dissection group were more likely to have grade 3 histology than those in the SLN group (34.7% vs 20.0%, p<0.001). The median total number of lymph nodes removed by any means (SLN+lymphadenectomy, pelvic or para-aortic) was higher in the lymphadenectomy group (26 and 4, respectively), as expected. No statistically significant difference was found in the use of adjuvant external beam radiation therapy between the lymphadenectomy and SLN groups (p=0.16), but patients in the lymphadenectomy group were more likely to have ever received external beam radiation therapy after surgery when reported at the time of the survey compared with the SLN group (51.5% vs 27.5%, p<0.001). The prevalence of lower extremity lymphedema at the time of the survey (defined as self-reported lower extremity lymphedema diagnosis or positive on screening questionnaire) was 37.6% and 25.8% for the lymphadenectomy and SLN groups, respectively (p=0.06). The median time between the date of surgery and the date in which patients filled out the survey was 2.5 (IQR 2.3–3.1) years in the lymphadenectomy group and 2.1 (IQR 1.5–2.5) years in the SLN group.

On comparing the functional and symptom QoL scale scores between the lymphadenectomy and SLN groups in an unadjusted analysis, a statistically significant difference was only observed for emotional functioning (assesses affective aspects of anxiety, depression, and general distress) (table 3). On achieving reasonable balance in the covariates between the groups in the adjusted cohort (see online supplemental table 1), the QoL scales were further analyzed. A statistically significant difference was only observed for emotional functioning in the adjusted analysis, with patients who underwent SLN having more favorable scores. The global QoL score was not significantly different with adjusted means of 80.6 and 78.8 in the two groups (p=0.44).

Multivariate analysis using the adjusted cohort was performed separately for each of the functioning and symptom QoL scales by including all variables (at the time of the survey) listed in the first column of table 4 in each model. Based on multivariate analysis, BMI, lower extremity lymphedema, and kidney disease had significant (p<0.05) and clinically meaningful negative impacts on QoL (table 4). Of note, the average adjusted global QoL score was 16.5 points lower (poorer) among patients with a history of kidney disease or failure compared with patients without this comorbidity at the time of survey. The impact of lower extremity lymphedema and comorbid obesity was particularly marked. In particular, the average adjusted global QoL score was 19.7 points lower (poorer) in morbidly obese (BMI ≥40 kg/m$^2$) patients with lower extremity lymphedema compared with non-obese patients without lower extremity lymphedema. In contrast, the adjusted average global QoL score was only 2.9 points different between the lymphadenectomy and SLN groups.

## DISCUSSION

### Summary of Main Results

Our data show lower extremity lymphedema, coupled with obesity, to be a strong predictor of poorer QoL in patients who underwent planned SLN staging for endometrial cancer. Nearly 15% of patients in the SLN group also underwent a side-specific lymphadenectomy, illustrating that our cohort was an adequate representation of clinical practice.[12] Comorbidity and comorbidity-associated lymphedema appear to drive reductions of QoL in these patients; thus, reducing the risk of lower extremity lymphedema attributable to endometrial cancer staging may contribute to improved QoL. When considering results from our prior study showing less lower extremity lymphedema in patients who undergo SLN as opposed to lymphadenectomy,[15] and our current results pointing to poorer QoL in patients with obesity and lymphedema, the benefit of SLN in these patients may become even more salient.

Lower extremity lymphedema is well-known to be a multifactorial process, which may explain why a robust difference does not exist in self-reported global QoL scores when examining surgical procedures alone. Our multivariable analysis showed that factors impacting QoL in patients undergoing primary surgery for endometrial cancer are lower extremity lymphedema and comorbidities such as obesity, and kidney disease or failure.

### Results in the Context of Published Literature

To our knowledge, this is the first study focusing on QoL in patients with endometrial cancer who are surgically staged using SLN biopsy. Previous studies have also shown an association between lower extremity lymphedema and poorer QoL.[6 16] An Italian group's comparison of patients who underwent surgery with or without systematic lymphadenectomy illustrated that lower extremity lymphedema interfered with patients' QoL as measured by the 24-item Quality of Life-Endometrial questionnaire, but the difference in 'Global health status' and 'Physical functioning' on the QLQ-C30 was not statisically significant between the two groups.[22] A study of 97 women who underwent minimally invasive surgery for endometrial cancer found no statistically significant difference between patients who underwent lymphadenectomy versus SLN biopsy.[23] Interestingly, in the SENTICOL-2 study there was a trend towards better QoL for patients who underwent SLN as opposed to SLN with lymphadenectomy for cervical cancer staging, concurring with our finding that emotional functioning/mental health was better in the SLN cohort.[24]

QoL is an important facet of endometrial cancer survivorship, which has been shown to be high with a 5-year relative survival rate for localized disease of 95%.[25] The incidence of endometrial cancer continues to rise, increasing the need for standardized approaches to comprehensively assess and intervene for issues

**Table 2** Summary of patient characteristics at the time of the surgery and at the time of the survey, by extent of nodal sampling

| Characteristic | LND group n=101 | SLN group n=120 | P* |
|---|---|---|---|
| At the time of the surgery | | | |
| Age (years), mean (SD) | 65.5 (7.9) | 64.0 (9.6) | 0.22 |
| BMI (kg/m$^2$), median (IQR) | 32.1 (26.2–37.5) | 33.6 (28.8–40.0) | 0.019 |
| BMI (kg/m$^2$), N (%) | | | 0.008 |
| <25.0 | 20 (19.8) | 9 (7.5) | |
| 25.0–29.9 | 23 (22.8) | 31 (25.8) | |
| 30.0–39.9 | 46 (45.5) | 49 (40.8) | |
| 40.0 or higher | 12 (11.9) | 31 (25.8) | |
| ASA score, N (%) | | | 0.55 |
| <3 | 80 (79.2) | 91 (75.8) | |
| ≥3 | 21 (20.8) | 29 (24.2) | |
| Comorbidities, N (%) | | | |
| Diabetes | 16 (15.8) | 15 (12.5) | 0.48 |
| Chronic heart failure | 1 (1.0) | 5 (4.2) | 0.22 |
| Moderate/severe renal disease | 2 (2.0) | 2 (1.7) | 0.99 |
| Surgical details | | | |
| FIGO grade, N (%) | | | <0.001 |
| 1 | 36 (35.6) | 75 (62.5) | |
| 2 | 30 (29.7) | 21 (17.5) | |
| 3 | 35 (34.7) | 24 (20.0) | |
| FIGO stage, N (%) | | | 0.26 |
| I/II | 90 (89.1) | 112 (93.3) | |
| III/IV | 11 (10.9) | 8 (6.7) | |
| Histology, N (%)† | | | 0.27 |
| Non-endometrioid | 19 (18.8) | 16 (13.3) | |
| Endometrioid | 82 (81.2) | 104 (86.7) | |
| Surgical staging approach, N (%) | | | <0.001 |
| Bilateral LND only, no SLN mapping attempted | 37 (36.6) | | |
| 'Backup' LND after SLN mapping | 64 (63.4)‡ | | |
| SLN removed, no LND | | 103 (85.8) | |
| SLN removed with unilateral side-specific LND | | 17 (14.2) | |
| Total nodes removed via SLN among those with nodes removed, median (IQR) | 2 (2–3)‡ | 3 (2–5) | <0.001 |
| LND performed, N (%) | | | <0.001 |
| No | – | 103 (85.8) | |
| Pelvic only | 56 (55.4) | 13 (10.8) | |
| Para-aortic only | – | 2 (1.7) | |
| Pelvic and para-aortic | 45 (44.6) | 2 (1.7) | |
| Total pelvic and para-aortic nodes removed via LND among those with nodes removed, median (IQR) | 26 (20–35) | 7 (4–9) | <0.001 |
| Total nodes removed by any means (SLN+LND), median (IQR) | 26 (20–35) | 4 (3–6) | <0.001 |
| Adjuvant therapy, N (%) | | | 0.26 |
| None or VB alone | 81 (80.2) | 103 (85.8) | |
| EBRT±VB | 2 (2.0) | 1 (0.8) | |
| Chemotherapy±VB | 11 (10.9) | 10 (8.3) | |
| Chemotherapy and EBRT±VB | 6 (5.9) | 2 (1.7) | |
| Unknown | 1 (1.0) | 4 (3.3) | |

Continued

**Table 2** Continued

| Characteristic | LND group n=101 | SLN group n=120 | P* |
|---|---|---|---|
| At the time of the survey | | | |
| Time between surgery and survey (years), median (IQR) | 2.5 (2.3–3.1) | 2.1 (1.8–2.5) | <0.001 |
| Age (years), mean (SD) | 68.3 (7.9) | 66.2 (9.6) | 0.09 |
| BMI (kg/m$^2$), median (IQR) | 30.1 (25.6–35.2) | 31.5 (28.0–37.6) | 0.04 |
| BMI (kg/m$^2$), N (%) | | | 0.04 |
| <25.0 | 22/97 (22.7) | 14/118 (11.9) | |
| 25.0–29.9 | 26/97 (26.8) | 35/118 (29.7) | |
| 30.0–39.9 | 44/97 (45.4) | 53/118 (44.9) | |
| 40.0 or higher | 5/97 (5.2) | 16/118 (13.6) | |
| Comorbidities, N (%) | | | |
| Diabetes | 28 (27.7) | 35 (29.2) | 0.81 |
| Chronic heart failure | 5 (5.0) | 10 (8.3) | 0.32 |
| Moderate/severe renal disease | 5 (5.0) | 4 (3.3) | 0.74 |
| Ever received EBRT or chemotherapy after surgery as treatment for primary or recurrence, N (%) | | | 0.003 |
| None | 46 (45.5) | 83 (69.2) | |
| EBRT alone | 35 (34.7) | 22 (18.3) | |
| Chemotherapy alone | 3 (3.0) | 4 (3.3) | |
| Chemotherapy and EBRT | 17 (16.8) | 11 (9.2) | |
| Ever diagnosed with a recurrence (based on self-report from survey or information in the medical record prior to the survey response date), N (%) | 9/100 (9.0) | 4/118 (3.4) | 0.08 |
| Lower extremity lymphedema, N (%) | 38 (37.6) | 31 (25.8) | 0.06 |
| Lower extremity lymphedema, by method of detection, N (%) | | | <0.001 |
| Reported being diagnosed but did not meet screening criteria at the time of the survey | 4 (4.0) | 0 (0.0) | |
| Met screener and reported being diagnosed | 17 (16.8) | 4 (3.3) | |
| Met screener only | 17 (16.8) | 27 (22.5) | |
| Not detected by any method | 63 (62.4) | 89 (74.2) | |

*Comparisons between the two groups were evaluated using the two-sample t-test for age, Wilcoxon rank-sum test for all other continuous or ordinal variables, and $\chi^2$ or Fisher's exact for categorical variables.
†Endometrioid histology includes endometrioid and mixed endometrioid and mucinous histology; non-endometrioid histology includes serous, clear cell, carcinosarcoma, mixed serous, and mixed clear cell.
‡Among these 64 patients in the LND group, 47 had SLN removed.
ASA, American Society of Anesthesiologists; BMI, body mass index; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; LND, lymphadenectomy; SLN, sentinel lymph node sampling; VB, vaginal brachytherapy.

related to QoL such as sexual health, physical activity, and sleep, among others.[26–29] The reduction of lower extremity lymphedema after surgical staging by performing SLN biopsy instead of lymphadenectomy provides a step in the right direction towards improving the lives of endometrial cancer survivors. This is especially true as obesity, the other risk factor in this equation, can be difficult to modify.[30] Future studies investigating relevant, just-in-time interventions for this population will further the positive change afforded by this surgical approach.

### Strengths and Weaknesses

The strengths of our study include a large sample size, which allowed detection of clinically meaningful differences in QoL between the staging groups. We also had longitudinal follow-up using validated questionnaires.[31] Limitations include the retrospective nature of this investigation, and the possibility that patients may have had pre-existing lymphedema before surgery that could not be captured in this format. In addition, patients with grade 3 disease may have been preferentially treated with lymphadenectomy early in the study protocol, possibly contributing to the difference in staging modality for these patients. Furthermore, because the surveys were mailed in 2016–2017, some of the earlier surgical cases may have already died at the time of survey, which could lead to a survival bias. Since it was not part of standard clinical practice to assess baseline QoL, it may have been worse in patients with higher BMI. To address this issue, we are currently conducting a prospective study examining baseline and subsequent QoL in patients with endometrial cancer.

### Implications for Practice and Future Research

Optimization of QoL in women treated for endometrial cancer represents a critical component of comprehensive

**Table 3** Comparison of functional and symptom quality of life scales by extent of nodal sampling, separately in the unadjusted and IPTW-adjusted cohorts

| | Unadjusted cohort | | | IPTW-adjusted cohort | | |
|---|---|---|---|---|---|---|
| **Scale** | **LND group (n=101)** | **SLN group (n=120)** | **P*** | **LND group (n=101)** | **SLN group (n=120)** | **P*** |
| Functional scales† | | | | | | |
| Global health status | | | 0.18 (0.61) | | | 0.44 |
| Mean (SD) | 80.8 (13.5) | 77.6 (19.9) | | 80.6 (12.7) | 78.8 (19.4) | |
| Median (IQR) | 83.3 (75.0–91.7) | 83.3 (66.7–91.7) | | 83.3 (75.0–91.7) | 83.3 (66.7–91.7) | |
| Score of 100, % | 12.9% | 16.7% | | 11.0% | 18.5% | |
| Physical functioning | | | 0.90 (0.83) | | | 0.91 |
| Mean (SD) | 87.9 (15.8) | 87.6 (17.8) | | 87.2 (16.2) | 87.5 (18.4) | |
| Median (IQR) | 93.3 (80.0–100.0) | 93.3 (86.7–100.0) | | 93.3 (80.0–100.0) | 93.3 (86.7–100.0) | |
| Score of 100, % | 42.6% | 44.2% | | 40.1% | 45.5% | |
| Role functioning | | | 0.76 (0.34) | | | 0.86 |
| Mean (SD) | 90.8 (17.4) | 91.5 (19.8) | | 90.9 (16.8) | 91.3 (20.3) | |
| Median (IQR) | 100.0 (83.3–100.0) | 100.0 (100.0–100.0) | | 100.0 (83.3–100.0) | 100.0 (100.0–100.0) | |
| Score of 100, % | 72.3% | 78.3% | | 72.5% | 78.3% | |
| Emotional functioning | | | 0.03 (0.09) | | | 0.03 |
| Mean (SD) | 88.9 (14.1) | 84.0 (18.7) | | 89.2 (13.7) | 84.4 (17.7) | |
| Median (IQR) | 91.7 (83.3–100.0) | 91.7 (75.0–100.0) | | 91.7 (83.3–100.0) | 91.7 (75.0–100.0) | |
| Score of 100, % | 42.6% | 38.3% | | 43.6% | 37.9% | |
| Cognitive functioning | | | 0.72 (0.83) | | | 0.98 |
| Mean (SD) | 88.9 (16.0) | 89.7 (16.5) | | 89.5 (15.6) | 89.5 (17.3) | |
| Median (IQR) | 100.0 (83.3–100.0) | 100.0 (83.3–100.0) | | 100.0 (83.3–100.0) | 100.0 (83.3–100.0) | |
| Score of 100, % | 57.4% | 55.8% | | 59.5% | 55.9% | |
| Social functioning | | | 0.35 (0.77) | | | 0.47 |
| Mean (SD) | 93.9 (13.9) | 91.7 (20.0) | | 93.7 (13.8) | 92.0 (19.7) | |
| Median (IQR) | 100.0 (100.0–100.0) | 100.0 (100.0–100.0) | | 100.0 (100.0–100.0) | 100.0 (100.0–100.0) | |
| Score of 100, % | 80.2% | 79.2% | | 79.5% | 80.3% | |
| Symptom scales and items‡ | | | | | | |
| Fatigue | | | 0.74 (0.93) | | | 0.70 |
| Mean (SD) | 18.3 (18.0) | 19.2 (19.5) | | 18.1 (17.4) | 19.0 (19.3) | |
| Median (IQR) | 11.1 (0.0–33.3) | 11.1 (0.0–33.3) | | 11.1 (0.0–33.3) | 11.1 (0.0–33.3) | |
| Score of 0, % | 30.7% | 31.7% | | 30.6% | 32.2% | |
| Pain | | | 0.91 (0.96) | | | 0.87 |
| Mean (SD) | 14.5 (20.6) | 14.9 (22.3) | | 14.3 (19.6) | 14.8 (22.3) | |
| Median (IQR) | 0.0 (0.0–33.3) | 0.0 (0.0–16.7) | | 0.0 (0.0–33.3) | 0.0 (0.0–16.7) | |
| Score of 0, % | 57.4% | 54.2% | | 56.7% | 54.6% | |
| Dyspnea, % | | | 0.92 (0.82) | | | 0.84 |
| 0 | 77.2% | 78.3% | | 76.5% | 78.0% | |
| 33.3 | 19.8% | 20.0% | | 20.2% | 20.4% | |
| 66.7 or 100 | 3.0% | 21.7% | | 3.3% | 1.6% | |

*Each scale was compared between the two groups based on fitting a linear regression model. In the unweighted analyses the p value in the parentheses is based on the non-parametric Wilcoxon rank-sum test.
†Higher functional scores indicate better functional well-being.
‡Higher symptom scores indicate worse symptom.
IPTW, inverse-probability of treatment weighting; LND, lymphadenectomy; SLN, sentinel lymph node sampling.

survivorship. Reducing the surgical contribution to lower extremity lymphedema prevalence with SNL biopsy as opposed to lymphadenectomy may improve QoL, especially in patients with elevated BMI. Prospective assessments of QoL including sexual health and subsequent targeted interventions introduce the promise of added benefits throughout a woman's treatment, and surveillance courses are ongoing.

## CONCLUSIONS

The main predictors of poorer QoL in patients surgically staged for endometrial cancer are lower extremity lymphedema and obesity.

**Table 4** Parameter coefficients from multivariable analysis of predictors of quality of life, evaluated separately for each of the functioning and symptom scales in the IPTW-adjusted cohort

| Variables included in each multivariable model | Functioning scales* | | | | | | Symptom scales† | |
|---|---|---|---|---|---|---|---|---|
| | Global QoL | Physical | Role | Emotional | Cognitive | Social | Fatigue | Pain |
| Intercept | 90.97‡ | 138.49‡ | 126.18‡ | 73.39‡ | 87.70‡ | 99.58‡ | 4.59 | −0.77 |
| Age at survey (years, reference is age 0) | −0.08 | −0.63‡ | −0.41‡ | 0.25‡ | 0.13 | −0.02 | 0.11 | 0.12 |
| LEL and BMI category | | | | | | | | |
| No LEL and BMI <30 (reference) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No LEL and BMI 30–39.9 | −6.52‡ | −5.27‡ | −2.89 | −2.61 | −1.92 | −2.02 | −0.32 | −1.00 |
| No LEL and BMI 40+ | −6.42 | **−10.97‡** | −7.33 | −3.80 | −4.00 | −0.20 | 3.56 | 0.70 |
| LEL and BMI <30 | −6.94 | −4.22 | **−12.47‡** | −7.32 | 0.41 | −4.54 | **10.03‡** | 9.03 |
| LEL and BMI 30–39.9 | **−18.13‡** | **−15.74‡** | **−12.64‡** | −8.17‡ | **−10.18‡** | **−13.75‡** | **18.83‡** | **19.48‡** |
| LEL and BMI at 40+ | **−19.70‡** | **−33.08‡** | **−31.11‡** | **−13.24‡** | **−22.19‡** | **−30.66‡** | **19.97‡** | **29.26‡** |
| History of diabetes at time of survey | 0.44 | −6.74‡ | −3.60 | −1.55 | −5.58‡ | −4.80 | 1.97 | 6.57‡ |
| History of heart failure or congestive heart failure at time of survey | **−6.25** | −4.39 | −0.48 | 1.74 | 6.21 | 1.44 | 0.07 | −8.69 |
| History of kidney disease or failure at time of survey | **−16.60‡** | −2.48 | −0.91 | **−14.12‡** | **−12.07‡** | −3.82 | **13.86‡** | **18.38‡** |
| Therapy received as treatment for primary cancer or recurrence | | | | | | | | |
| None (reference) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EBRT alone | 0.74 | 1.38 | 0.13 | −2.00 | −2.48 | 2.04 | 2.21 | 0.98 |
| Chemotherapy±EBRT | 0.28 | −4.44 | −3.15 | −5.40 | **−10.24‡** | −3.75 | 5.83 | 2.23 |
| Type of staging | | | | | | | | |
| SLN biopsy (reference) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LND | 2.87 | 0.59 | 0.35 | 5.14‡ | 0.79 | 2.53 | −2.71 | −1.83 |

QoL scores range from 0 to 100.
Bold indicates clinically meaningful difference (≥10 points).
*Higher functional scores indicate better functional well-being.
†Higher symptom scores indicate worse symptom.
‡Statistically significant, p<0.05.
BMI, body mass index (kg/m$^2$) at time of survey; EBRT, external beam radiation therapy; IPTW, inverse-probability of treatment weighting; LEL, lower extremity lymphedema; LND, lymphadenectomy; QoL, quality of life; SLN, sentinel lymph node.

**Author affiliations**
[1]Dipartimento per la Salute della Donna e del Bambino e della Salute Pubblica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[2]Department of Gynecologic Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy
[3]Health Sciences Research, Mayo Clinic Rochester, Rochester, Minnesota, USA
[4]Department of Gynecologic Oncology, Cleveland Clinic, Cleveland, Ohio, USA
[5]Gynecologic Surgery, Mayo Clinic, Rochester, Minnesota, USA
[6]Division of Biomedical Statistics and Informatics, Mayo Clinic Rochester, Rochester, Minnesota, USA
[7]Physical Medicine and Rehabilitation, Mayo Clinic Rochester, Rochester, Minnesota, USA

**Correction notice** This article has been corrected since it was first published to amend the second affiliation.

**Twitter** Francesco Multinu @Fmultinu

**Acknowledgements** We thank the staff of the Mayo Clinic Survey Research Center for their help in designing and implementing the survey and for entering survey responses using double data entry procedures.

**Contributors** GD: conceptualization, data curation, formal analysis, writing - original draft preparation; FM: data curation, formal analysis, methodology; KY: data curation, formal analysis, methodology; MAH: writing - review and editing; AL: writing - review and editing; CL: writing - review and editing; AK: writing - review and editing; ALW: data curation, formal analysis, methodology, writing - review and editing; MEM: data curation, formal analysis, methodology; writing - review and editing; AC: writing - review and editing; SCD: writing - review and editing; AM: conceptualization, writing - review and editing; GG: guarantor, conceptualization, supervision, writing - review and editing.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by IRB Application #: 09-004517. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on request. In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**ORCID iDs**
Francesco Multinu http://orcid.org/0000-0001-8535-4059
Carrie Langstraat http://orcid.org/0000-0001-9361-8392
Amanika Kumar http://orcid.org/0000-0002-1470-1305
Andrea Mariani http://orcid.org/0000-0001-8059-1602
Gretchen Glaser http://orcid.org/0000-0001-9413-316X

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