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Lymphedema After Surgery for Endometrial Cancer: Prevalence, Risk Factors, and Quality of Life

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Abstract

Objective—To estimate lower-extremity lymphedema prevalence in patients surgically treated for endometrial cancer, identify predictors of lymphedema, and evaluate the effects of lymphedema on quality of life.

Methods—One thousand forty-eight consecutive patients who were operated on between 1999 and 2008 at Mayo Clinic were mailed a survey, which included our validated 13-item lymphedema screening questionnaire and two validated quality-of-life measures. Logistic regression models were fit to identify factors associated with prevalent lymphedema; a multivariable model was obtained using stepwise and backward variable selection methods. The relationship between lymphedema and obesity with each quality-of-life score was evaluated in a separate multivariable linear model.

Results—There were 591 responders (56%) after exclusions. Our questionnaire revealed a previous self-reported lymphedema diagnosis in 103 (17%) patients and identified undiagnosed lymphedema in 175 (30%) (overall prevalence 47.0%; median 6.2 years follow-up). Lymphedema prevalence in patients treated with hysterectomy alone compared with lymphadenectomy was 36.1% and 52.3%, respectively (attributable risk, 23%). Lymphedema risk was not associated with the number of nodes removed or the extent of lymphadenectomy after adjusting for other factors. On multivariable analysis, higher BMI, congestive heart failure, performance of lymphadenectomy, and radiation therapy were associated with prevalent lymphedema. Multiple quality-of-life scores were worse in women with lymphedema.

Conclusion—The attributable risk of developing lower-extremity lymphedema was 23% for patients with endometrial cancer who underwent lymphadenectomy compared to hysterectomy

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alone, with an overall prevalence of 47%. Lymphedema was associated with reductions in multiple quality-of-life domains.

Introduction

Surgical lymphadenectomy and radiation are common components of therapy for women with endometrial cancer and are thought to increase the risk of developing lower-extremity lymphedema. These patients may also have comorbid conditions such as obesity that further increase their risk. Once present, the symptoms and local effects of lymphedema can only be managed, not cured. The resulting disability may lead to severe lifelong morbidity including pain, skin breakdown, impaired mobility, difficulty with self-care, psychosocial morbidity, and impaired quality-of-life (1–3).

Current estimates of the prevalence and burden of lower-extremity lymphedema in patients with endometrial cancer are unreliable due to a requirement for extended prospective follow-up. Signs and symptoms are often ignored or unrecognized, and the diagnosis may be challenging because the condition is frequently bilateral, prohibiting comparison with an uninvolved contralateral limb (in contrast to upper extremity lymphedema in the context of axillary lymphadenectomy for breast cancer) (4). Furthermore, it may be difficult to distinguish adiposity from lymphedema, particularly in obese patients. We undertook this investigation because understanding the likelihood of lower-extremity lymphedema and its impact on quality-of-life is critically important for proper patient counseling, timely treatment, and assessment of the pros and cons of therapies which may result in lymphedema.

Recognizing that patient-reported symptoms accompany and often precede the onset of objective swelling (5), we recently developed and validated a 13-question, lower-extremity lymphedema screening questionnaire to characterize prevalence (6). This validated instrument was administered together with quality-of-life surveys to a large endometrial cancer cohort with extended follow-up in order to ascertain the prevalence of lymphedema, its effect on function and quality of life, and to identify risk factors for lower-extremity lymphedema.

Materials and Methods

Between January 5, 1999 and December 18, 2008, 1,415 patients underwent surgery for endometrial cancer at Mayo Clinic, Rochester. As part of an ongoing investigation, patient-specific, disease-specific, and treatment-specific risk factors were abstracted from the medical records by a dedicated registered nurse over the same time period following the American College of Surgeons' National Quality Improvement Program platform (7). These data were later rechecked by members of our research team to confirm accuracy. Adequacy of lymphadenectomy was defined as removal of at least 10 pelvic nodes and at least 5 PA nodes (8, 9). The Mayo Foundation Institutional Review Board approved this investigation to contact patients for additional follow-up between November 2010 and July 2011.

The 1,048 living 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 lymphedema, quality-of-life surveys (European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality of Life in Cancer questionnaire (QLQ-C30) and the EORTC 24-item Endometrial Cancer module (EN-24)), and a 13-item lower-extremity lymphedema screening questionnaire that we validated previously in 127 women (see the Appendix, available online at <http://links.lww.com/xxx>)(6, 10). Importantly, the validation set for our screening questionnaire was stratified by body mass index to ensure its performance in both obese and non-obese women. Sensitivity and specificity were 95.5% and 86.5%, respectively (94.8% and 76.5% for body mass index ≥ 30 kg/m²). If no response was received after one month, a second survey was mailed. Patients were contacted by phone and encouraged to complete the survey if, after a second month, it had not been returned. Mailing of the surveys occurred between June 17, 2011 and December 15, 2011 (note that the December 15 mailing was for a single patient to re-send the HIPAA form). Survey response dates ranged from June 23, 2011 to January 25, 2012. Data specialists from the Mayo Clinic Survey Research Center entered the data from the returned surveys; data was triple-checked for accuracy. Patients who returned surveys for this investigation were subsequently provided with information on lymphedema and given contacts for evaluation.

Data were summarized using standard descriptive statistics. Patient characteristics were compared between groups (in study vs. not in study vs. deceased; hysterectomy alone vs. hysterectomy and lymphadenectomy) using the F-test from a one-two ANOVA model or two-sample t-test for age, Kruskal-Wallis test or Wilcoxon rank-sum test for other continuous variables, and the chi-square test for categorical variables. For patients in study, univariable logistic regression models were fit to separately evaluate individual factors associated with prevalent lymphedema. A multivariable logistic regression model was identified using stepwise and backward variable selection methods considering all variables with a p-value <0.20 based on the univariable analysis. Associations were summarized by calculating odds ratios (ORs) and corresponding 95% confidence intervals (CIs) from the model parameter estimates. The risk of lower-extremity lymphedema attributable to lymphadenectomy was calculated as follows: $[\text{Probability}(\text{lymphedema}) - \text{Probability}(\text{lymphedema} \mid \text{Hysterectomy only})] / \text{Probability}(\text{lymphedema})$, where $\text{Probability}(\text{lymphedema})$ was estimated based on the prevalence of lower-extremity lymphedema.

Nine functional and symptom scales from the 30-item Quality of Life in Cancer questionnaire were analyzed. For each outcome scale, a multivariable linear regression model was fit to evaluate the impact on each quality-of-life outcome of lymphedema alone, obesity alone, and lymphedema and obesity together after adjusting for age, stage, duration of follow-up, external beam irradiation therapy, and comorbidities. Clinical significance was defined as a difference in a quality-of-life outcome of 10 or more points on a 0–100 point scale (11). All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS software package (version 9.2; SAS Institute, Inc.; Cary, NC).

Results

Of the original cohort of 1,415 patients with endometrial cancer, 358 deceased patients and 9 patients who had requested not to be contacted were not considered for study. Surveys were mailed to the remaining 1048 patients, of whom 648 (61.8%) responded. Fifty-seven patients were excluded for the following reasons: preoperative history of lymphedema (n=19); answering an insufficient number of the screener questions, defined as 6 or fewer (i.e., 50%) of the 13 questions (n=27); did not indicate if a physician or nurse had diagnosed lymphedema (n=10); radical orthopedic resection of the pelvis three years after surgery for endometrial cancer which would be expected to result in lymphedema (n=1; the boney resection was for an indication other than endometrial cancer and the patient had no evidence of lymphedema prior to that resection). After exclusions there were 591 patients (56.4%) in the final sample. Median time from surgery to survey response was 6.2 years (interquartile range 4.2–8.9 years) and 21.7% had a body mass index ≥ 40 kg/m² at the time of their surgery. Table 1 contrasts the characteristics of the 591 women included in this study (“in study”) versus the 358 women deceased at the time of the survey mailing and the remaining 466 women (“not in study”) who either did not respond to the survey (n=400), were not contacted (n=9), or were excluded as described above (n=57). Deceased patients were significantly older, more likely to have congestive heart failure within 30 days prior to surgery, had higher grade and more advanced stage disease, and were treated significantly more frequently with lymphadenectomy as well as external beam irradiation. Patients who were not in study had similar rates of radiotherapy, higher body mass index, were more likely to have diabetes at the time of the surgery, and had slightly lower rates of lymphadenectomy compared to those in the study.

Patient characteristics of patients included in study are shown in Table 2 stratified by lymphadenectomy. As previously described, our division utilizes objective pathologic factors to select patients for lymphadenectomy (12, 13). Lymphadenectomy is omitted for patients with all four of the following tumor characteristics: tumor diameter less than 2cm, less than 50% myometrial invasion, grade 1 or 2, and endometrioid histology. Thus, 191 patients (32.3%) of the 591 women included in this study underwent hysterectomy alone because they met Mayo Clinic’s low-risk criteria or were not candidates for lymphadenectomy secondary to comorbidities or advanced disease, whereas 400 (67.7%) had hysterectomy with pelvic and/or para-aortic lymphadenectomy.

Examining the study cohort of 591 women, our survey identified undiagnosed lower-extremity lymphedema in 29.6% (n=175). An additional 17.4% (n=103) self-reported having a lymphedema diagnosis by a clinician after surgery (patients with lymphedema diagnosed prior to surgery were excluded *a priori*). Thus, the overall prevalence of lymphedema was 47%, reflecting the long median follow-up of 6.2 years. Time from surgery to survey did not differ when comparing the 103 patients who self-reported a diagnosis of lymphedema after surgery versus the remaining in study patients (median, 6.5 vs. 6.1 years, p=0.98).

The prevalence of lower-extremity lymphedema (defined as self-reported lymphedema diagnosis after surgery or screen positive on our lymphedema screening questionnaire) was

36.1% in patients treated with hysterectomy alone compared with 52.3% for hysterectomy with lymphadenectomy. The risk of lymphedema attributable to lymphadenectomy was calculated as 23%. Furthermore, a self-reported diagnosis of lymphedema was made in 23.3% of patients who underwent lymphadenectomy compared to 5.2% who did not. A total of 454 patients (77%) responded that their surgeon had not discussed the possibility of developing lymphedema as a result of their endometrial cancer surgery. The possibility of lymphedema was discussed preoperatively in 40 (7%) and 97 (16%) either did not answer the question or answered that they did not know.

Table 3 summarizes characteristics that were evaluated separately for an independent association with prevalent lower-extremity lymphedema. All individual characteristics with a P value <0.20 were then allowed to compete in backwards and stepwise modeling. Obesity, congestive heart failure, performance of lymphadenectomy, and use of external beam irradiation therapy were identified as significantly associated with prevalent lymphedema in the resulting multivariable model (Table 4).

Within the lymphadenectomy cohort, we compared rates of lymphedema in 290 patients who had both an adequate pelvic and para-aortic lymphadenectomy against 85 patients in whom an adequate pelvic lymphadenectomy was performed, but para-aortic lymphadenectomy was omitted. The risk of lymphedema was no higher among women who had an adequate pelvic and para-aortic lymphadenectomy compared to an adequate pelvic lymphadenectomy alone (52.4% vs. 49.4%; $p=0.63$), suggesting that the extent of dissection beyond the pelvis does not impact development of lymphedema. The number of patients with an inadequate pelvic lymphadenectomy ($n=10$) or an inadequate para-aortic lymphadenectomy ($n=13$) or both ($n=2$) in our series was too small to assess for an association between adequacy of lymphadenectomy and lower-extremity lymphedema.

Multivariable models were fit for each of the functional and symptom scales of the 30-item Quality of Life in Cancer questionnaire to evaluate the relationship of presence of lymphedema and obesity with each scale after adjusting for age, stage, duration of follow-up, external beam irradiation therapy and comorbidities. Higher scores are indicative of better functional well-being, whereas for the symptom scores, higher scores are indicative of worse symptoms. As shown in Table 5, lymphedema had a greater adverse impact on quality-of-life scores than body mass index. All strata that included women with lymphedema, regardless of body mass index, were statistically significantly worse ($p<0.05$) compared to the reference group of non-obese women without lymphedema. In addition, the majority of the quality-of-life scores in patients with lymphedema were also *clinically* significantly worse compared to the reference group, as indicated by a score difference equal to or greater than the minimally important difference of 10 points (11). For example, after adjusting for the other variables, the average global quality-of-life score was 11.8 points lower in non-obese patients *with* lymphedema compared to non-obese patients *without* lymphedema, which is an indication of the impact on quality-of-life of lymphedema alone in the absence of obesity. In contrast, global quality-of-life scores for obese (body mass index 30 to <40) and morbidly obese (body mass index ≥ 40) patients *without* lymphedema were only 3.5 and 4.0 points lower, respectively, compared to non-obese patients *without* lymphedema; differences that were neither statistically nor clinically significant. These

comparisons thus reflect the impact on quality-of-life of body mass index alone, in the absence of lower-extremity lymphedema. Adverse impacts on quality-of-life were greatest in women with both lymphedema and obesity or morbid obesity. Patients with lymphedema also reported worse endometrial cancer-specific domains on the 24-item Endometrial Cancer module (e.g., lymphedema symptoms, urological symptoms, body image, back/pelvic pain $p<0.001$; sexual functioning $p<0.05$).

Discussion

Here we demonstrate that lower-extremity lymphedema is present in nearly half of surveyed endometrial cancer survivors and is associated with clinically significant reductions in nearly every quality-of-life domain tested, irrespective of body mass index. In addition to radiation therapy, obesity, and congestive heart failure, lymphadenectomy was independently associated with prevalent lower-extremity lymphedema in multivariable analysis with an attributable risk of 23%. These findings are important, recognizing that patients with endometrial cancer frequently live long enough to develop delayed side effects associated with treatment. The association of lymphadenectomy with high rates of lymphedema and accompanying reductions in quality of life, along with the reported higher cost of care, higher short-term morbidity, and a lack of survival benefit for low-risk patients cast further doubt on the value of what is most certainly surgical over-treatment for the majority of patients (12, 14, 15). Few of our patients recalled being advised of the risks of lymphedema, signaling a need to improve preoperative counseling.

Strategies to reduce lymphedema include omission of lymphadenectomy in low risk patients (16–20). Sentinel lymph node mapping (21) has also been utilized, but preliminary data suggest it may be unacceptably high for patients at high risk (22), and according to the most accepted algorithm 35–50% of patients who undergo sentinel lymph node dissection will nevertheless require unilateral or even bilateral lymphadenectomy. Interestingly, we found no relationship between the number of lymph nodes removed or the extent of lymphadenectomy (pelvic vs. pelvic and para-aortic dissection) with development of lymphedema after adjusting for other risk factors in a multivariable analysis. These findings are consistent with other reports (23–24). Long-term assessments are therefore obligatory to demonstrate reductions in lymphedema for patients who undergo sentinel lymph node mapping (25). Finally, several investigations have shown that preservation of the distal most external iliac lymph node at the circumflex vein may reduce lymphedema (26–27). However, the median body mass index in these Japanese cohorts was only 22, and patients with radiation were excluded from analysis, indicating the need to validate this theory in obese patients and in those requiring adjuvant therapies.

Prior studies have identified a wide range of lymphedema prevalence (1–38%) using numerous means of assessment and various lengths of follow-up (2, 28–32). Strengths of our investigation include the use of a validated instrument to detect lower-extremity lymphedema that was confirmed to perform well in obese patients (6). While some may consider leg circumference measurements the gold standard, patient-reported symptoms are known to precede the onset of clinically detectable lymphedema (5). Compared to prior investigations, our cohort was large, limited to patients with endometrial cancer, and

included a median follow-up of over 6 years. Predetermined criteria for the use of lymphadenectomy as described previously limits potential bias (12, 13). Finally, we used validated instruments to assess quality of life in patients with lymphedema and a diagnosis of endometrial cancer.

Weaknesses include the absence of information on the severity of lymphedema. While our instrument was designed to measure severity, this has not yet been validated. However, the large differences in multiple quality-of-life domains suggest that detection of lymphedema by our survey was indeed clinically relevant. Although our lymphedema instrument may have overestimated the prevalence of lymphedema given its specificity was 76% in the obese validation cohort, this may be balanced by response bias. Patients who were deceased at the time our survey was administered were more likely to have advanced disease and 2–3 times more likely to have received radiation therapy, placing them at significantly higher risk of developing lymphedema. We did not inquire about the onset of symptoms in relation to surgery because we believed this would be highly inaccurate due to recall bias. Lastly, although in most cases lower extremity lymphedema is bilateral in the context of bilateral lymphadenectomy for endometrial cancer, we did not specifically inquire if symptoms were unilateral or bilateral.

In addition to prospectively assessing the incidence and risk factors of lymphedema, the ongoing Gynecologic Oncology Group LEG study (GOG 244, The Lymphedema and Gynecologic Cancer Study) will assess quality of life in 1,300 patients with endometrial, vulvar, and cervical cancer. This will provide critical information for counseling and consideration of pros and cons of surgical and medical treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of patients in study, not in study, and those deceased

Characteristic	In Study	Not in Study	Deceased	<i>p</i> [†]
	n=591	n=466	N=358	
Age at time of surgery (years), mean (SD)	61.8 (10.3)	63.0 (11.7)	70.3 (11.5)	<0.001
BMI at time of surgery (kg/m ²), mean (IQR)	31.4 (25.9,38.7)	33.3 (27.0,40.0)	30.8 (25.6,36.5)	<0.001
BMI at time of surgery (kg/m ²), N (%)				0.004
Underweight or normal (BMI<24.9)	124 (21.0)	75 (16.1)	75 (21.1)	
Overweight (BMI 25.0–29.9)	138 (23.4)	91 (19.6)	90 (25.3)	
WHO class I/II (BMI 30.0–39.9)	201 (34.0)	181 (38.9)	137 (38.5)	
WHO class III/super obese (BMI 40.0–49.9/50+)	128 (21.7)	118 (25.4)	54 (15.2)	
Comorbidities, N (%)				
History of diabetes at time of the surgery	106 (17.9)	111 (23.8)	75 (20.9)	0.06
CHF within 30 days prior to the surgery	2 (0.3)	2 (0.4)	8 (2.2)	0.004
History of renal failure at time of the surgery	1 (0.2)	5 (1.1)	5 (1.4)	0.08
Surgical details				
FIGO grade, n (%)				<0.001
1	308 (52.1)	269 (57.7)	78 (21.8)	
2	172 (29.1)	113 (24.3)	80 (22.3)	
3	111 (18.8)	84 (18.0)	200 (55.9)	
FIGO stage, n (%)				<0.001
I/II	541 (91.5)	421 (90.3)	168 (46.9)	
III/IV	50 (8.5)	45 (9.7)	190 (53.1)	
LND, N (%)				0.003
No	191 (32.3)	181 (38.8)	99 (27.7)	
Yes	400 (67.7)	285 (61.2)	259 (72.3)	
Total nodes removed, median (IQR)	32 (0,53)	26 (0,48)	29 (0,46)	0.06
Pelvic LND, N (%)				0.004
No	193 (32.7)	183 (39.3)	102 (28.5)	
Yes	398 (67.3)	283 (60.7)	256 (71.5)	
Total pelvic nodes removed, median (IQR)	25 (0,38)	21 (0,34)	23 (0,33)	0.02
Para-aortic LND, N (%)				0.09
No	285 (48.2)	244 (52.4)	160 (44.7)	
Yes	306 (51.8)	222 (47.6)	198 (55.3)	
Total para-aortic nodes removed, median (IQR)	4 (0,15)	0 (0,14)	4 (0,13)	0.43
External beam irradiation therapy, N (%)	42 (7.1)	30 (6.4)	63 (17.6)	<0.001

BMI, body mass index; CHF, congestive heart failure; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LND; lymphadenectomy; SD, standard deviation; WHO, World Health Organization.

[†]F-test *P*-value from 1-way ANOVA presented for age, Kruskal-Wallis test *p*-values presented for all other continuous variables and chi-square test *P*-values presented for categorical variables. *P*-values less than 0.0033 ($=0.05/15$) are considered statistically significant after Bonferroni correction for multiple comparisons.

Table 2

Characteristics of in Study Patients Stratified by Lymphadenectomy

Characteristic	Hysterectomy Alone	Hysterectomy and Pelvic and/or Para-aortic LND	<i>p</i> [†]
	n=191	n=400	
Age at time of surgery (years)			0.007
Mean (SD)	60.2 (10.8)	62.6 (10.0)	
Median (IQR)	59.8 (53.3, 67.6)	63.1 (56.0, 69.6)	
BMI at time of surgery(kg/m ²)			0.22
Mean (SD)	33.8 (9.9)	32.7 (9.0)	
Median (IQR)	32.8 (26.2, 39.9)	31.1 (25.9, 38.1)	
Time from surgery to survey (years)			0.28
Mean (SD)	6.8 (2.8)	6.5 (2.8)	
Median (IQR)	6.4 (4.3, 9.2)	6.1 (4.2, 8.8)	
FIGO grade, N (%)			<0.001
1	153 (80.1)	155 (38.8)	
2	28 (14.7)	144 (36.0)	
3	10 (5.2)	101 (25.3)	
FIGO stage, N (%)			<0.001
I/II	188 (98.4)	353 (88.3)	
III	1 (0.5)	37 (9.3)	
IV	2 (1.0)	10 (2.5)	
Total nodes removed			–
Mean (SD)	–	48 (23)	
Median (IQR)	–	46 (32, 62)	
Total pelvic nodes removed			–
Mean (SD)	–	35 (15)	
Median (IQR)	–	34 (25, 44)	
Total para-aortic nodes removed			–
Mean (SD)	–	16 (9)	
Median (IQR)	–	15 (10, 21)	
External beam irradiation therapy, N (%)	2 (1.0)	40 (10.0)	<0.001

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LND; lymphadenectomy; SD, standard deviation.

[†] Two-sample t-test p-value presented for age, Wilcoxon rank-sum p-values presented for all other continuous variables, and chi-square p-values presented for categorical variables.

Table 3

Univariable Predictors of Lower-Extremity Lymphedema

Characteristic	No LEL	LEL	Univariate Odds Ratio (95% CI)	p†
	n=313	n=278		
Age at the time of surgery (years), mean (SD) *	61.4 (10.4)	62.4 (10.3)	1.10 (0.94, 1.29)	0.23
BMI at the time of surgery (kg/m ²), median (IQR) *	29.7 (24.8, 34.7)	34.3 (27.4, 41.8)	1.32 (1.20, 1.46)	<0.001
BMI at the time of surgery (kg/m ²)				<0.001
Underweight or normal (BMI<24.9)	80 (25.6)	44 (15.8)	Reference	
Overweight (BMI 25.0–29.9)	85 (27.2)	53 (19.1)	1.13 (0.69, 1.88)	
WHO class I/II (BMI 30.0–39.9)	110 (35.1)	91 (32.7)	1.50 (0.95, 2.39)	
WHO class III/super obese (BMI 40.0–49.9/50+)	38 (12.1)	90 (32.4)	4.31 (2.54, 7.30)	
Comorbidities				
Diabetes or high blood sugar	92 (29.4)	104 (37.4)	1.44 (1.02, 2.03)	0.04
CHF	12 (3.9)	27 (9.7)	2.70 (1.34, 5.43)	0.006
Kidney disease or failure	6 (1.9)	16 (5.8)	3.13 (1.21, 8.10)	0.02
Time from surgery to survey (years), median (IQR)	6.1 (4.3, 9.0)	6.4 (4.1, 8.7)	0.99 (0.94, 1.05)	0.79
FIGO grade				0.09
1	175 (55.9)	133 (47.8)	Reference	
2	88 (28.1)	84 (30.2)	1.26 (0.86, 1.83)	
3	50 (16.0)	61 (21.9)	1.61 (1.04, 2.48)	
FIGO stage				0.001
I/II	298 (95.2)	243 (87.4)	Reference	
III/IV	15 (4.8)	35 (12.6)	2.86 (1.53, 5.36)	
LND				<0.001
No	122 (39.0)	69 (24.8)	Reference	
Yes	191 (61.0)	209 (75.2)	1.94 (1.36, 2.76)	
Total nodes removed, median (IQR) *	28 (0, 50)	35 (0, 55)	1.03 (1.00, 1.06)	0.02
Pelvic LND				<0.001
No	122 (39.0)	71 (25.5)	Reference	
Yes	191 (61.0)	207 (74.5)	1.86 (1.31, 2.65)	
Total pelvic nodes removed, median (IQR) *	23 (0, 38)	27 (0, 38)	1.05 (1.00, 1.09)	0.03
Para-aortic LND				0.005
No	168 (53.7)	117 (42.1)	Reference	
Yes	145 (46.3)	161 (57.9)	1.59 (1.15, 2.21)	
Total para-aortic nodes removed, median (IQR) *	0 (0, 14)	6 (0, 16)	1.08 (1.00, 1.17)	0.05
External beam irradiation therapy	12 (3.8)	30 (10.8)	3.03 (1.52, 6.05)	0.002

BMI, body mass index; CHF, congestive heart failure; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LND; lymphadenectomy; WHO, World Health Organization.

Percent based on nonmissing values. Mean (SD) presented for continuous variables and n (%) presented for categorical variables.

* Odds ratios per 10-year increase in age, per 5-unit increase in BMI, and per 5-node increase for total, pelvic and para-aortic node removal.

† P-values are presented based on fitting univariate logistic regression models. P-values less than 0.0031 ($=0.05/16$) are considered statistically significant after Bonferroni correction for multiple comparisons.

Table 4

Multivariable Analysis of Predictors of Lower-Extremity Lymphedema

Characteristic	Adjusted Odds Ratio (95% CI)	P
BMI at the time of surgery (kg/m ²)		<0.001
Underweight or normal (BMI<24.9)	Reference	
Overweight (BMI 25.0–29.9)	1.11 (0.66, 1.87)	
WHO class I/II (BMI 30.0–39.9)	1.45 (0.90, 2.34)	
WHO class III/super obese (BMI 40.0–49.9/50+)	4.69 (2.71, 8.13)	
Congestive heart failure	2.58 (1.23, 5.40)	0.01
Lymphadenectomy	2.04 (1.39, 2.99)	<0.001
External beam irradiation therapy	3.00 (1.46, 6.16)	0.003

Note: Odds ratios shown are adjusted for each of the other characteristics listed in this table.

BMI, body mass index; WHO, World Health Organization.

Table 5
Multivariable Analysis of Predictors of the Quality of Life in Cancer Questionnaire (QLQ-C30) Functional Scales and Symptom Scales

Variables Includes in Each Multivariable Model	Functioning Scales						Symptom Scales/Items		
	Global QOL	Physical Function	Role Function	Emotional Function	Cognitive Function	Social Function	Fatigue	Pain	Dyspnea
Intercept	91.2	129.1	124.1	73.6	83.0	105.5	-1.2	-5.7	-10.4
LEL/BMI classification at the time of the survey									
No LEL, BMI <30 kg/m ²	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
LEL, BMI <30 kg/m ²	-11.8*	-9.0	-8.4	-12.0*	-10.1*	-13.1*	18.2*	15.1*	9.5
No LEL, BMI 30–39 kg/m ²	-3.5	-5.1	-1.5	-0.18	-1.5	-1.9	4.1	5.1	6.6
LEL, BMI 30–39 kg/m ²	-13.1*	-16.2*	-11.5*	-8.4	-8.7	-8.2	16.3*	16.5*	15.4*
No LEL, BMI 40 kg/m ²	-4.0	-9.2	-2.7	-3.1	6.0	-6.2	2.6	9.7	1.9
LEL, BMI 40 kg/m ²	-22.1*	-31.6*	-25.9*	-15.1*	-9.0	-21.5*	26.7*	29.4*	27.1*
Age at survey (per 5 years)	-0.50	-2.5	-2.0	1.4	0.56	-0.62	1.1	0.79	0.82
FIGO stage III/IV (vs. I/II)	-2.5	0.04	-2.9	-2.8	-7.0	1.1	1.6	-7.1	-4.0
Time from surgery to survey (per 5 years)	-0.01	-1.1	-1.1	-1.7	-1.2	0.04	-1.2	2.3	1.9
External beam irradiation therapy (vs. no)	2.0	-1.6	-1.3	3.3	5.3	-5.8	-0.28	0.65	4.9
Heart failure or CHF (vs. no)	-8.5	-10.8*	-11.2*	-3.1	-2.1	-8.9	6.4	0.02	16.1*
Kidney disease or failure (vs. no)	-5.0	-6.9	-15.0*	-6.7	-7.4	-8.9	7.9	3.5	0.46
Diabetes or high blood sugar (vs no)	-3.1	-1.2	0.93	-1.0	2.1	-3.1	-0.01	0.65	0.27

BMI, body mass index; CHF, congestive heart failure; FIGO, International Federation of Gynecology and Obstetrics; LEL, lower-extremity lymphedema.

P<0.05 for values in boldface type.

* Meets or exceeds the minimally important difference of 10 points and denotes clinically significant differences.

[†] Higher functional scores indicate better functional well-being.

[‡] Higher symptom scores indicate worse symptom

The regression coefficients for the variables included in the nine multivariable models are summarized in the table. All functional[†] and symptom[‡] scales were significantly worse in women with lower-extremity lymphedema.