

## Self-reported lower extremity lymphedema and quality of life after surgical staging of endometrial carcinoma: A population based cross-sectional study

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### HIGHLIGHTS

- Lymphedema is more prevalent after lymphadenectomy compared to sentinel lymph node biopsy.
- Adding sentinel lymph node to hysterectomy does not increase the prevalence of lymphedema.
- Lower extremity lymphedema is associated with lower quality of life.
- Questionnaires may not distinguish symptoms of lymphedema from musculoskeletal complaints.

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### ABSTRACT

**Objectives.** Sentinel lymph node biopsy (SLN) has replaced lymphadenectomy in staging of endometrial carcinoma. The aims of the study were to explore the prevalence of self-reported lymphedema (LEL), identify factors associated with LEL, compare quality of life (QoL) scores using thresholds of clinical importance, and assess correlation between different questionnaires.

**Methods.** Women who underwent staging for endometrial carcinoma from 2006 to 2021 were invited to complete the Lower Extremity Lymphedema Screening Questionnaire (LELSQ), EORTC QLQ-C30, QLQ-EN24 and EQ-5D-5L.

**Results.** Of 2156 invited survivors, 61% participated in the study, whereof 1127 were evaluable by LELSQ. The LEL prevalence was 51%, 36% and 40% after lymphadenectomy, SLN and hysterectomy, respectively ( $p < 0.001$ ). Higher BMI, undergoing lymphadenectomy and receiving adjuvant chemotherapy were associated with LEL; odds ratios 1.07 (95% CI 1.05–1.09), 1.42 (95% CI 1.03–1.97) and 1.43 (95% CI 1.08–1.89) respectively. QoL was lower for women with LEL compared to those without. In women *with* musculoskeletal complaints the prevalence of LEL was 59%, 50% and 53% after lymphadenectomy, SLN and hysterectomy ( $p = 0.115$ ), respectively, compared to 39%, 17% and 18% ( $p < 0.001$ ) in women *without* musculoskeletal complaints. Spearman's correlation was moderate to strong between the questionnaires.

**Conclusion.** SLN implementation is not associated with increased LEL prevalence compared to hysterectomy alone, but is associated with a significantly lower prevalence compared to lymphadenectomy. LEL is associated with lower QoL. Our study demonstrates moderate to strong correlation between self-reported LEL and QoL

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scores. Available questionnaires may not distinguish between symptoms caused by LEL and musculoskeletal disease.

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## 1. Introduction

Most women diagnosed with endometrial carcinoma present at an early stage, carrying good prognosis [1]. Recommended treatment for assumed early-stage endometrial carcinoma is minimally invasive hysterectomy, bilateral salpingo-oophorectomy with or without nodal assessment [2]. Lower extremity lymphedema (LEL) is a long-term complication after several cancer treatments, including endometrial carcinoma [3]. Replacing lymphadenectomy (LND) with a sentinel lymph node algorithm (SLN), has showed a reduction in risk of developing LEL [4,5]. Other risk factors for LEL are older age, increased body mass index (BMI) and adjuvant chemo-radiation therapy [6–8]. There is no gold standard for measuring or reporting LEL. Several methods exist, including patient-reported outcome measures (PROMs). LEL prevalence is reported from three to 70% using various measuring tools [4,6,8–10].

Previous studies have demonstrated reduced Quality of Life (QoL) in women with LEL [7,8,11,12]. The European Organisation for Research and Treatment of Cancer (EORTC) QoL group has recently established thresholds for clinical importance of absolute scores in order to better interpret differences in scores from individual patients at a single point in time [13]. Comparison of QoL applying these thresholds for clinically important changes has not previously been reported for endometrial carcinoma survivors.

The primary aim of this study is to explore the post-operative prevalence of self-reported LEL in endometrial carcinoma survivors stratified by nodal assessment, and to identify risk factors associated with the development of LEL. Secondary aims are to compare QoL scores using thresholds of clinical importance, and assess correlation between PROMs tools.

## 2. Materials and methods

This study was approved by Regional Committees for Medical and Health Research Ethics in South East and Central Norway (References 149,597 and 7193/2019). All women provided informed consent. Data were handled in accordance with relevant ethical regulations.

This multicenter, population-based cross-sectional study included women treated for assumed early-stage endometrial carcinoma from 2006 to 2021 at Oslo University Hospital (OUH) and 2012 to 2021 at St. Olav's Hospital. Both hospitals are tertiary referral centers for gynecologic cancers, covering 66% of the Norwegian population and were selected as they represent the only regions where the SLN approach was implemented during the study period (Supplemental Fig. 1). Both institutions use the Memorial Sloan Kettering Cancer Centre (MSKCC) SLN algorithm [14]. Nodal assessment was defined as *hysterectomy* if no nodal assessment was performed, as *SLN* if the MSKCC SLN algorithm was adhered to and as *lymphadenectomy (LND)* if pelvic LND with or without para-aortic LND was performed. The cohorts were mutually exclusive.

A power calculation was performed prior to study start. With a two-sided significance level of 5% and a power of 90%, 227 patients were needed in each group to detect a 15% difference in prevalence of lower extremity lymphedema between cohorts. This absolute difference was based on the expected LEL prevalence of 35% in the SLN and hysterectomy cohorts and 50% in the lymphadenectomy cohort based on previous studies. This was less than the number of potential respondents (2156 women) and allows adjusting for several potential confounding variables in this observational design setting.

### 2.1. Patient-reported outcome measures

A mixed-mode survey design was used to optimize participation rate (Fig. 1). The survey included questions regarding demographics, comorbidities and the LELSQ. In order to evaluate QoL by a cancer-specific, diagnosis-specific and generic PROMs tool; EORTC QLQ-C30, EORTC QLQ-EN24 and EQ-5D-5L were selected [15–17].

### 2.2. LELSQ

LELSQ is a validated questionnaire consisting of 13 graded questions. At least seven questions must be answered to be evaluable [18]. Self-reported LEL was defined as scoring  $\geq 5$  points out of 52 possible points on LELSQ or being diagnosed with LEL by health care professionals. Only women with newly developed LEL after surgery were included, i.e. patients with a diagnosis of LEL prior to surgery were not included in this analysis. LELSQ was chosen in order to compare results with previously published studies [7,8,18–20]. Our group has translated and tested LELSQ in a Norwegian population [21].

### 2.3. EQ-5D-5L

EQ-5D-5L<sup>17</sup> measures health status in five domains, using five levels in each domain. The EQ-5D-5L answer-set is transformed into a QoL-index from 0 to 1, using the EQ-5D-5L scoring manual [22]. We used the British value set [23] in this study and denoted the index as Quality Adjusted Life Year weight (QALYw). EQ-5D-5L also includes a visual analog scale (VAS) ranging from 0 (“the worst health you can imagine”) to 100 (“the best health you can imagine”), where death is not included on the scale.

### 2.4. EORTC QLQ-C30 and EORTC QLQ-EN24

EORTC QLQ-C30 [24] and EORTC QLQ-EN24 [16] are developed to evaluate QoL in cancer patients. QLQ-C30 consists of 30 items structured into a global health status/QoL scale, five functional scales, three symptom scales, and six single items. QLQ-EN24 consists of 24 endometrial carcinoma-specific items structured into ten symptom scales and three functional scales. All questions are graded; “none”, “a little”, “quite a bit” or “very much”. The scoring of the QLQ-C30 and QLQ-EN24 were performed according to scoring manual of the EORTC QoL group [15]. Thresholds of clinical importance was defined according to the EORTC QoL Group where scale scores of EORTC QLQ-C30 were dichotomized into categories over or under the thresholds of clinical importance [13].

Demographics, comorbidities, tumor- and treatment-related factors were extracted from electronic medical records. A modified version of the Self-Administered Comorbidity Questionnaire [25] adding “deep venous thrombosis”, was used to collect self-reported comorbidities at survey [26]. *Musculoskeletal complaints* was defined as arthritis and/or back pain and/or rheumatoid arthritis. Follow-up time was defined as months from surgery to first invitation to survey.

### 2.5. Statistical analysis

Descriptive statistics were provided for baseline variables. Categorical variables were presented as frequencies and proportions, continuous variables as mean with standard deviation (SD) or median with



**Fig. 1.** Flow chart showing timeline for participation recruitment.

A mixed-mode survey design was used to optimize participation rate. The first mailing included study information and an invitation to participate in an online survey. Invited women were informed that a paper version of the questionnaire would be mailed to non-responders after electronic reminders. Non-responders were reminded by text messages containing direct links to the online survey two and four weeks later. Finally, a paper version with a pre-paid envelope was distributed to non-responders one month after the final text message.

interquartile range (IQR). Comparison of cohorts stratified by nodal assessment (hysterectomy, SLN and LND) or LEL status (negative/positive) was performed by chi2 test, *t*-test or ANOVA and Mann-Whitney or Kruskal-Wallis tests, as appropriate.

Logistic regression analysis was used to investigate associations of baseline covariates with self-reported LEL. Variables included in the multivariable model were BMI at surgery, nodal assessment and adjuvant therapy. Nodal count and histology were omitted from the model due to their high correlation with nodal assessment and adjuvant treatment.

To further explore a potential relationship with musculoskeletal complaints and LEL, regression analysis was stratified by presence or absence of musculoskeletal complaints. In addition to investigating type of nodal assessment, we also considered the number of nodes removed. A log transformation was applied due to its non-linear relationship with LEL.

Relationship between the global health status/QoL scale and QALYv and VAS, and participants' individual scores from LELSQ and the lymphedema domain in EORTC QLQ-EN24 were assessed by Spearman's correlation coefficient with 95% confidence interval (CI) calculated by bootstrap estimation. A correlation coefficient of 0.40–0.69 was considered as moderate, and > 0.70 as strong.

The significance level was set to  $p < 0.05$ . Stata/SE 17.0 was used for statistical analysis.

### 3. Results

Of 2156 invited survivors, 1226 (61%) responded to the survey (Fig. 2). Responders were younger, had shorter follow-up, lower BMI at surgery and received more adjuvant chemotherapy than non-responders (Supplement Table 1). Of responders, 90/1226 were not evaluable by LELSQ. Two patients underwent para-aortic LND alone and were excluded from further analysis. The remaining 1134 responders were stratified according to nodal assessment; 35% underwent LND, 34% SLN and 31% hysterectomy (Supplemental Table 2). The SLN-cohort was older at surgery and younger at survey. There was no significant difference in BMI between cohorts. SLN mapping was bilateral in 80% and unilateral in 15% of women.

Regarding self-reported comorbidities at time of survey, no statistically significant differences were observed between cohorts (data not shown).

Median number of lymph nodes removed was 21 (IQR 14–28) and three (IQR 2–5) in the LND and SLN cohorts, respectively. More patients in the LND cohort received adjuvant therapy. No significant difference in recurrence was detected when comparing LND and SLN cohorts; 8% and 5% respectively ( $p = 0.18$ ).

#### 3.1. Lymphedema

The LELSQ was evaluable for 1127 women, where the overall LEL-prevalence was 42%. For the LND- SLN- and hysterectomy cohorts the prevalence was 51%, 36% and 40% respectively ( $p < 0.001$ ) (Table 1).

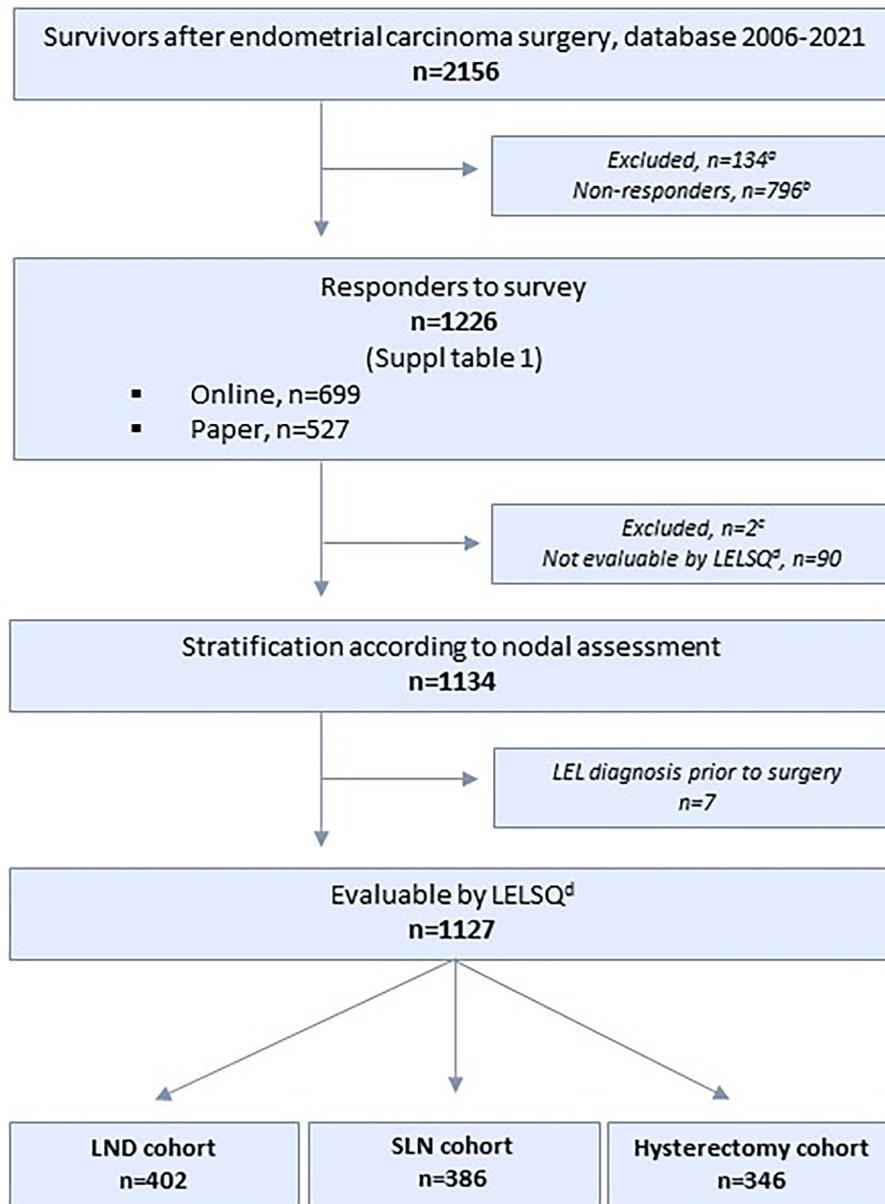
Mean age at survey was 71.2 years, not differing between groups. LEL-positive women had longer follow-up; 70 vs 62 months ( $p = 0.006$ ), higher BMI; 29.9 vs 27.6 ( $p < 0.001$ ), and were more frequently diagnosed with hypertension at surgery; 42% vs 34% ( $p = 0.005$ ) than LEL-negative women. For self-reported comorbidities at survey; hypertension, ulcer/stomach disease, anemia/blood disease, depression, arthritis, back pain, rheumatoid arthritis, deep venous thrombosis/pulmonary embolism and “other disease/health complaint” were more common in the LEL-positive group. There was no difference between groups regarding FIGO stage. In the LEL-positive group, a median of four lymph nodes (IQR 0–19) were removed, compared to three (IQR 0–10) in the LEL-negative group ( $p < 0.005$ ). Women with self-reported LEL more often received adjuvant chemotherapy. Eight of 1127 (<1%) patients received adjuvant radiotherapy, three in the LEL-negative group and five in the LEL-positive group.

When exploring associations of LEL, adjusting for relevant variables in the multivariate model; BMI at surgery (per one unit increase), LND (hysterectomy as reference) and adjuvant chemotherapy remained significantly associated with LEL; OR 1.07 (95% CI 1.05–1.09), OR 1.42 (95% CI 1.03–1.97), and OR 1.43 (95% CI 1.08–1.89) respectively (Table 2).

Musculoskeletal complaints were reported by 637 (56%) of responders (Table 1), of which 98% reported that musculoskeletal problems affected activities of daily living (data not shown). Women who self-reported musculoskeletal complaints were older and had higher BMI (data not shown).

When stratifying by musculoskeletal complaints (Fig. 3); for women with musculoskeletal complaints, the prevalence of self-reported LEL did not differ between nodal assessment cohorts; 59%, 50% and 53% after LND, SLN and hysterectomy, respectively ( $p = 0.115$ ). For women without musculoskeletal complaints the prevalence of self-reported LEL did differ between nodal assessment cohorts; 39%, 17%, 18% for LND, SLN and hysterectomy, respectively ( $p < 0.001$ ). The prevalence of self-reported LEL was significantly lower for women without musculoskeletal complaints when compared to women with musculoskeletal complaints in the corresponding nodal assessment cohort; 39% vs 59%, 17% vs 50% and 18% vs 53% for LND, SLN and hysterectomy, respectively ( $p < 0.001$ ) (Fig. 3).

Further, for women with musculoskeletal complaints, BMI and adjuvant chemotherapy were significantly associated with scoring positive for LEL, while type of nodal assessment was not (Table 2). For women



**Fig. 2.** Consort flow chart showing study recruitment.

(LEL = Lower extremity lymphedema, LELSQ = Lower Extremity Lymphedema Screening Questionnaire, LND = Lymphadenectomy, SLN = Sentinel lymph node biopsy, PALND=Para-aortic lymphadenectomy).

without musculoskeletal complaints, BMI and LND were significantly associated with scoring positive for LEL (Table 2).

In further analysis, using the log of number of nodes removed, there was a positive association with LEL (OR 1.24, 95% CI 1.08–1.42). BMI and adjuvant chemotherapy remained significant in this model (Supplement Table 3).

### 3.2. Quality of life

Women with LEL had significant more problems compared to women without LEL, in all domains of QLQ-C30 (Table 3). The proportion of patients with LEL over or under the threshold for clinical importance for functional and symptoms scales, ranged from 6% (appetite loss) to 74% (physical functioning).

Median QALYw and VAS scores were 0.94 and 80 for LEL-negative women, and 0.81 and 65 for LEL-positive women ( $p < 0.001$ ) (Supplemental Table 4).

Compared to LEL negative women, LEL-positive women scored significantly lower in all domains of EORTC QLQ-C30 and EORTC QLQ-EN24, except sexual enjoyment and sexual interest (Supplemental Table 2).

The relationship between participants' LELSQ scores and EORTC QLQ-EN24 lymphedema domain scores was strong; Spearman's correlation coefficient 0.83 (95% CI 0.81–0.85). The relationship between EORTC QLQ-C30 global health status/QoL scale, and QALYw and VAS were moderate; 0.67 (95% CI 0.63–0.71) and 0.79 (95% CI 0.76–0.81) (Supplemental Table 4).

## 4. Discussion

### 4.1. Principal findings

In this unselected population, 42% of women scored positive for LEL after surgical staging for endometrial carcinoma. Prevalence of LEL was

**Table 1**  
Clinicopathological characteristics according to self-reported lower extremity lymphedema (LEL).

Demographic characteristics	Evaluable by LELSQA	LEL negative	LEL positive	p-value
	n = 1127	n = 651 (58%)	n = 476 (42%)	
<b>Age at surgery</b> (years), mean (SD)	64.5 (9.4)	64.4 (9.0)	64.6 (9.9)	p = 0.790
<b>Follow-up time</b> (months), median (interquartile)	71 (39–122)	62 (29–107)	70 (38.5–122.5)	p = 0.006
<b>Age at survey</b> (years), mean (SD)	71.2 (9.2)	70.8 (8.9)	71.7 (9.2)	p = 0.124
<b>BMI at surgery</b> (m/kg <sup>2</sup> ), mean (SD) n = 1092	28.6 (6.2)	27.6 (5.8)	29.9 (6.6)	p < 0.001
<b>Self-reported BMI at survey</b> (m/kg <sup>2</sup> ), n = 1099	28.0 (5.7)	27.1 (5.2)	29.4 (6.1)	p < 0.001
<b>Comorbidities at surgery</b>				
Hypertension n = 1127	421 (37%)	221 (34%)	200 (42%)	p = 0.005
Diabetes mellitus n = 1127	110 (10%)	61 (9%)	49 (10%)	p = 0.432
COPD n = 1127	26 (2%)	12 (2%)	14 (3%)	p = 0.220
Coronary artery disease n = 1127	31 (3%)	18 (3%)	13 (3%)	p = 0.985
Previous deep venous thrombosis or Pulmonary Embolism n = 1127	32 (3%)	15 (2%)	17 (4%)	p = 0.202
Dementia or cognitive impairment n = 1127	1 (<1%)	1 (<1%)	0	p = 0.394
Cerebrovascular disease or Transitory Ischemic Attack n = 1121	30 (3%)	17 (3%)	13 (3%)	p = 0.874
<b>Self-reported comorbidities at survey</b>				
Self-reported hypertension n = 1069	469 (41%)	245 (38%)	224 (47%)	p = 0.001
Self-reported ulcer/stomach disease n = 1016	21 (2%)	7 (1%)	14 (3%)	p = 0.016
Self-reported anemia or other blood disease n = 1013	35 (3%)	11 (2%)	24 (5%)	p = 0.001
Self-reported depression n = 1015	150 (13%)	66 (10%)	84 (18%)	p < 0.001
Self-reported arthritis <sup>b</sup> n = 1048	445 (39%)	190 (29%)	255 (54%)	p < 0.001
Self-reported back pain n = 1042	431 (38%)	189 (29%)	242 (51%)	p < 0.001
Self-reported rheumatoid arthritis n = 1007	69 (6%)	20 (3%)	49 (10%)	p < 0.001
Self-reported deep venous thrombosis/pulmonary embolism n = 1018	64 (6%)	28 (4%)	36 (7%)	p = 0.010
Other disease/health complaint <sup>c</sup> n = 896	343 (30%)	159 (24%)	184 (38%)	p < 0.001
Muscle/skeletal complaints combined (arthritis/back pain/rheumatoid arthritis) <sup>d</sup> n = 1078	637 (56%)	292 (45%)	345 (72%)	p < 0.001
Self-reported heart disease n = 1026	129 (13%)	71 (11%)	58 (12%)	p = 0.357
Self-reported lung disease n = 1015	102 (9%)	52 (8%)	50 (10%)	p = 0.099
Self-reported diabetes mellitus n = 1030	154 (14%)	85 (13%)	69 (14%)	p = 0.389
Self-reported renal disease n = 1008	22 (2%)	10 (2%)	12 (3%)	p = 0.194
Self-reported liver disease n = 1009	4 (<1%)	2 (<1%)	2 (<1%)	p = 0.709
Self-reported cancer (other than endometrial) n = 1034	242 (22%)	142 (22%)	100 (21%)	p = 0.909
<b>Final stage (FIGO 2009)</b>				
I	953 (84%)	563 (86%)	390 (82%)	
II	49 (4%)	25 (4%)	24 (5%)	
III (A + B)	28 (2%)	14 (2%)	14 (3%)	
III C	88 (8%)	43 (7%)	45 (9%)	
IV	9 (<1%)	6 (1%)	3 (<1%)	
<b>Final histology</b>				p = 0.001
Endometrioid	865 (76%)	523 (80%)	342 (72%)	
Non-endometrioid	262 (23%)	128 (20%)	134 (28%)	
<b>Nodal assessment</b>				p < 0.001
Hysterectomy	344 (31%)	208 (32%)	136 (29%)	
SLN algorithm	385 (34%)	246 (38%)	139 (29%)	
LND	398 (35%)	197 (30%)	201 (42%)	
<b>Nodes removed</b>				
Median (interquartile), n = 1122	3 (0–15)	3 (0–10)	4 (0–19)	p = 0.005
<b>Adjuvant therapy</b>				p = 0.006
None	727 (65%)	442 (68%)	285 (60%)	
Chemotherapy only	384 (34%)	199 (31%)	185 (39%)	
Radiotherapy w/wo chemo	8 (<1%)	3 (<1%)	5 (1%)	
Unknown/missing	8 (<1%)	7 (1%)	1 (<1%)	
<b>Recurrence</b>				p = 0.169
No	1054 (94%)	615 (94%)	439 (92%)	
Yes	65 (6%)	30 (5%)	34 (7%)	
Unknown/missing	9 (<1%)	6 (1%)	3 (<1%)	

<sup>a</sup> Lower Extremity Lymphedema Screening Questionnaires.

<sup>b</sup> Osteoarthritis or degenerative arthritis.

<sup>c</sup> Other disease/health complaint is not further specified.

<sup>d</sup> Minimum one of the three complaints.

higher in women after LND than after SLN or hysterectomy, and similar for the SLN- and hysterectomy-cohorts. Other independent risk factors for LEL were increasing BMI and adjuvant chemotherapy. In women who self-reported musculoskeletal complaints, nodal assessment did not influence self-reported LEL.

Women with LEL reported lower QoL in all domains of EORTC QLQ-C30 assessed by a novel threshold for clinical importance, not previously assessed for endometrial carcinoma survivors. The correlations between EORTC QLQ-C30 global health status/QoL scale and QALYw and VAS by EQ-5D-5L, and the correlation between LELSQ and the EORTC QLQ-EN24 lymphedema domain were all moderate to strong.

## 5. Results in the context of what is known

### 5.1. Adding a SLN algorithm to hysterectomy alone does not increase prevalence of LEL

The higher prevalence of LEL in women after LND compared to SLN or hysterectomy alone are in line with previous studies [7,8]. Our findings of similar prevalence of LEL after SLN and hysterectomy alone are not previously reported in large studies. Unlike previous studies, women with failed mapping undergoing uni- or bilateral side-specific LND are included in the SLN-cohort as per intention-

**Table 2**  
Multivariable logistic regression analysis for scoring positive for lower extremity lymphedema, also stratified by musculoskeletal complaints, n = 1122.

Characteristics	Total	Musculoskeletal complaints	No musculoskeletal complaints
	OR (95% CI)	OR (95% CI)	OR (95% CI)
BMI at surgery (kg/m <sup>2</sup> ) <sup>a</sup>	1.07 (1.05–1.09)	1.06 (1.03–1.09)	1.05 (1.01–1.09)
LND <sup>b,c</sup>	1.42 (1.03–1.97)	1.15 (0.74–1.78)	2.64 (1.47–4.75)
SLN <sup>b,d</sup>	0.75 (0.54–1.03)	0.73 (0.48–1.12)	0.82 (0.44–1.53)
Chemotherapy <sup>e</sup>	1.43 (1.08–1.89)	1.49 (1.02–2.15)	1.18 (0.70–1.96)

OR = odds ratio, CI = confidence interval.

<sup>a</sup> One unit increase.

<sup>b</sup> Hysterectomy as reference.

<sup>c</sup> LND = Pelvic +/- para-aortic lymphadenectomy.

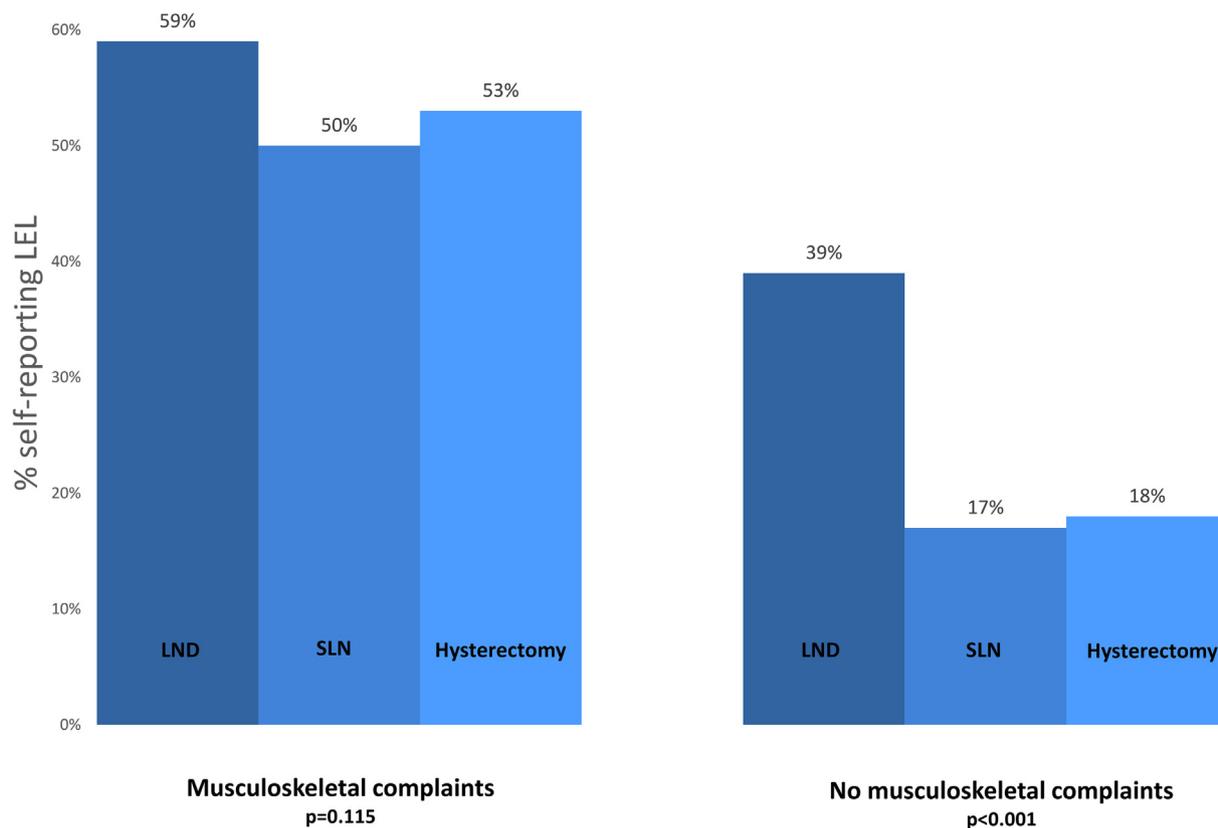
<sup>d</sup> SLN = Sentinel Lymph Node Biopsy.

<sup>e</sup> No adjuvant therapy as reference.

to-treat, irrespective of number of nodes removed [7,8,10]. The reported prevalence of LEL after surgery and adjuvant chemotherapy in this mainly radiotherapy-naïve population is in line with previously published findings, indicating that receipt of any adjuvant therapy may negatively influence development of LEL. Forsse et al. described an increased lymphedema score after adjuvant chemotherapy compared to nodal staging without chemotherapy [12]. This differs from our findings where both LND and adjuvant chemotherapy were associated with LEL. Despite chemotherapy being more commonly administered in the SLN cohort compared to hysterectomy, this does not seem to increase LEL prevalence for the SLN cohort.

### 5.2. Musculoskeletal complaints may mimic LEL symptoms

To our knowledge, no previous studies have reported the prevalence of musculoskeletal disease in endometrial carcinoma survivors and its potential influence on scoring positive for LEL. In our study, the prevalence of underlying musculoskeletal complaints is in line with the general population of elderly females in Norway (50%) [27]. Questions used to capture LEL in the LELSQ are similar to symptoms commonly reported by patients with musculoskeletal disease such as pain, stiffness and swelling. [Miller, 1990 #348] Due to overlapping symptoms of musculoskeletal complaints and LEL, the LELSQ may be unable to differentiate between these conditions.



**Fig. 3.** Bar chart showing the prevalence of LEL stratified by musculoskeletal complaints.

For women with musculoskeletal complaints the prevalence of self-reported LEL did not differ between nodal assessment cohorts. For women without musculoskeletal complaints the prevalence of self-reported LEL did differ between nodal assessment cohorts.

The prevalence of self-reported LEL was significantly lower for women without musculoskeletal complaints when compared to women with musculoskeletal complaints in the corresponding nodal assessment cohort ( $p < 0.001$ ).

(LEL = Lower extremity lymphedema, LND = Lymphadenectomy, SLN = Sentinel lymph node biopsy).

**Table 3**

Quality of Life measured by EORTC QLQ-C30 reported as the % of women under or over the threshold for clinical importance determined by the EORTC QoL group.

	LEL negative n = 651 (58%)	LEL positive n = 476 (42%)	p-value
<b>Functional scale</b>	% of women under threshold determined by EORTC Quality of Life group		
Physical functioning n = 1095	34%	74%	p < 0.001
Role functioning n = 1109	7%	28%	p < 0.001
Emotional Functioning n = 1092	13%	33%	p < 0.001
Cognitive function n = 1004	15%	34%	p < 0.001
Social function n = 1107	8%	27%	p < 0.001
<b>Symptom scale</b>	% of women over threshold determined by EORTC QoL group		
Fatigue n = 1102	18%	50%	p < 0.001
Nausea and vomiting n = 1110	10%	25%	p < 0.001
Pain n = 1100	27%	69%	p < 0.001
Dyspnea n = 1117	30%	57%	p < 0.001
Sleep disturbance n = 1117	17%	37%	p < 0.001
Appetite loss n = 1116	3%	6%	p < 0.002
Constipation n = 661	8%	18%	p < 0.001
Diarrhea n = 1111	28%	44%	p < 0.001
Financial difficulties n = 1108	7%	20%	p < 0.001

P-values describe the statistical differences between LEL positive and negative women.

This hypothesis is supported by our finding that type of nodal assessment (LND, SLN or hysterectomy alone) was *not* associated with scoring positive for LEL in women *with* self-reported musculoskeletal complaints (Fig. 3). It is also supported by the finding of significant differences in prevalence of women scoring positive for LEL after hysterectomy and SLN in women with and without self-reported musculoskeletal disease. In our study, 17% and 18% of women *without* musculoskeletal complaints scored positive for LEL after SLN or hysterectomy. This prevalence is lower than for those with musculoskeletal disease where 50% and 53% scored positive for LEL after SLN and hysterectomy respectively. This is also lower than previously published results from cross-sectional studies in an American population; 27% after SLN<sup>8</sup> and 36% after hysterectomy [7].

### 5.3. QoL is lower in women with LEL according to a novel threshold for clinical importance

Previous studies report differences in QoL by statistically significant levels [8] or by  $\geq 10$  points difference as described by Osoba [7]. We compared QoL by a novel method for interpretation of the EORTC QLQ-C30 score; *threshold for clinical importance*. We believe this method adds a more clinically meaningful interpretation of scores.

### 5.4. EQ-5D-5L and EORTC QLQ-C30 can be considered comparable for QoL evaluation

Comparing EORTC QLQ-C30 scores to EQ-5D-5L in endometrial carcinoma survivors has not previously been reported. As demonstrated in our study, nodal assessment is correlated to development of LEL with subsequent detriment to QoL. Based on our results, QALYw and VAS as per EQ-5D-5L can be considered comparable to EORTC QLQ-C30 when reporting QoL. We demonstrated a strong correlation between participants' individual LELSQ scores and EORTC QLQ-EN24 lymphedema specific domain scores.

## 6. Clinical implications

Patients with endometrial carcinoma scheduled for staging surgery should be counselled regarding increasing BMI as a possibly modifiable risk factor for LEL. The potential risk of LEL after SLN biopsy should not be used to argue against implementation of an SLN algorithm, even in assumed low-risk patients, as similar prevalence of self-reported LEL are seen in women after hysterectomy alone and SLN. The risk of LEL

is associated with each additional lymph node removed, highlighting the importance of successful *bilateral* SLN mapping, thus limiting nodal removal to only sentinel lymph nodes in contrast to multiple nodes removed for lymphadenectomy.

Adjuvant chemotherapy was significantly associated with LEL and should be limited to women who will truly benefit from it. This can be achieved by further developing individual treatment algorithms incorporating predictive and prognostic biomarkers, molecular classification, and alternative targeted therapies.

## 7. Research implications

In our study, women who scored positive for LEL more often self-report musculoskeletal complaints, possibly reflecting overlapping risk factors for development of LEL and musculoskeletal disorders such as increasing BMI and age, as well as overlapping symptoms. This relationship has not been described previously and should be investigated further. As cross-sectional studies are hypothesis generating, we hypothesize that the PROMs used in this study may not be able to capture LEL alone, but actually capture musculoskeletal complaints as well. Questionnaires for LEL are commonly developed based on questionnaires intended for breast cancer survivors [18,28]. Musculoskeletal complaints may not overlap with symptoms and risk factors for upper extremity lymphedema. Creation and validation of PROMs capturing LEL should address this.

## 8. Strengths and limitations

This is a large population-based study regarding self-reported LEL and QoL in endometrial carcinoma survivors. Importantly, this study had a robust response rate and was performed in a public health care system with an unselected patient population.

The retrospective design is a limitation with its inherent biases. Although the non-randomized study design may be a limitation, nodal assessment groups were equally represented in this study, and responders did not vary greatly from non-responders regarding known characteristics. Some non-responders may be too frail to respond to the questionnaire, and thus not be represented in the LEL and QoL data. This limitation could lead to a general overestimation of QoL in EC survivors. The shorter follow-up of the SLN cohort may be considered a weakness. The median follow-up for all cohorts is however more than two years after initial therapy, which is the time-period when LEL commonly develops [6].

Clinical examination and objective measurements would strengthen the results. This was not feasible for this large population, but is planned in a future intervention study for a selected group of women. Overall, the results from our study are robust, and we await the results from ENDO3 with its randomized, prospective design, for comparison [29].

## 9. Conclusions

Our study confirms that risk factors associated with self-reported post-operative LEL are higher BMI, receiving adjuvant chemotherapy and undergoing LND. LEL is associated with lower QoL. The addition of a SLN algorithm to hysterectomy alone does not increase the risk of LEL, and should not be used as an argument against implementation of SLN in this patient population.

Interestingly, the prevalence of LEL may not be as high as previously reported in endometrial carcinoma survivors, as underlying musculoskeletal disorders could mimic LEL signs and symptoms. This relationship should be further explored.

## Author contributions

All authors revised and agreed on the final version to be submitted.

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#### Tweetable statement

Women with lymphedema after endometrial carcinoma surgery report reduced quality of life, however musculoskeletal complaints may mimic lymphedema symptoms cautioning interpretation of results from PROMs.

#### Declaration of Competing Interest

Ane Gerda Z Eriksson reports receiving speakers' fees from Intuitive surgical and GSK. Other authors report no conflict of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2023.05.070>.

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