Does sentinel node mapping impact morbidity and quality of life in endometrial cancer?

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ABSTRACT

Objectives To evaluate the prevalence of post-operative complications and quality of life (QoL) related to sentinel lymph node (SLN) biopsy vs systematic lymphadenectomy in endometrial cancer.

Methods A prospective cohort included women with early-stage endometrial carcinoma who underwent lymph node staging, grouped as follows: SLN group (sentinel lymph node only) and SLN+LND group (sentinel lymph node biopsy with addition of systematic lymphadenectomy). The patients had at least 12 months of follow-up, and QoL was assessed by European Organization for Research and Treatment of Cervical Cancer Quality of Life Questionnaire 30 (EORTC-QLQ-C30) and EORTC-QLQ-Cx24. Lymphedema was also assessed by clinical evaluation and perimetry.

Results 152 patients were included: 113 (74.3%) in the SLN group and 39 (25.7%) in the SLN+LND group. Intra-operative surgical complications occurred in 2 (1.3%) cases, and all belonged to SLN+LND group. Patients undergoing SLN+LND had higher overall complication rates than those undergoing SLN alone (33.3% vs 14.2%; p=0.011), even after adjusting for confound factors (OR=3.45, 95% CI 1.40 to 8.47; p=0.007). The SLN+LND group had longer surgical time (p=0.001) and need for admission to the intensive care unit (p=0.001). Moreover, the incidence of lymphocele was found in eight cases in the SLN+LND group (0 vs 20.5%; p<0.001). There were no differences in lymphedema rate after clinical evaluation and perimetry. However, the lymphedema score was highest when lymphedema was reported by clinical examination at 6 months (30.1 vs 7.8; p<0.001) and at 12 months (36.3 vs 6.0; p<0.001). Regarding the overall assessment of QoL, there was no difference between groups at 12 months of follow-up.

Conclusions There was a higher overall rate of complications for the group undergoing systematic lymphadenectomy, as well as higher rates of lymphocele and lymphedema according to the symptom score. No difference was found in overall QoL between SLN and SLN+LND groups.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the growing evidence of SLN mapping in endometrial cancer, prospective studies addressing morbidity and impact on QoL are lacking.

WHAT THIS STUDY ADDS

⇒ We prospectively addressed morbidity and QoL in patients that underwent SLN compared to SLN with backup lymphadenectomy.

⇒ We found that the addition of lymphadenectomy to SLN biopsy significantly increased the early complication rates and lymphedema according to the symptom score.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While the results of prospective trials on SLN biopsy are still waited, the present study supports SLN biopsy as a staging method with lower surgical complication rates.

INTRODUCTION

Endometrial cancer is the most common malignancy of the female genital tract in developed countries,[1] and lymph node dissection has been considered as part of endometrial cancer staging since the seminal Gynecologic Oncology Group GOG-33 study, though never being the study's aim.[2]

Conversely, sentinel lymph node (SLN) biopsy has emerged as an acceptable and accurate surgical strategy for endometrial cancer staging even for high-grade histologies.[3 4] SLN assessment potentially prevents the early morbidity associated with a systematic lymphadenectomy, such as neurovascular injury and lymphocyst formation.[5] Moreover, late morbidity, such as lower limb lymphedema, can also be avoided, leading to a better treatment experience and quality of life.[6 7]

Only recent data support a high prevalence of lower limb lymphedema after uterine cancer treatment. In early-stage cervical cancer, the SENTIREC study reported a prevalence of lower limb lymphedema in 5.6% for women who underwent the SLN mapping compared with 32.2% after the addition of pelvic lymphadenectomy.[8] Moreover, a large retrospective endometrial cancer series evaluated patients undergoing SLN and noted a lower rate of patient-reported

lymphedema than with lymphadenectomy (27% vs 41%, p=0.002).[9]

Cancer treatment has a major negative impact on a woman's life. In this scenario, the high level of psychological stress has profound negative repercussion on the quality of life (QoL), mainly in the first year of treatment, for patients, partners, and family members.[10] Therefore, improvement of surgical morbidity knowledge in gynecological cancer surgery and how complications are valued by patients, and its impact on global health might help health providers to deliver tailored support and treatment.[11]

Despite the growing evidence of SLN mapping in endometrial cancer, prospective studies addressing morbidity and impact on QoL are still lacking.[12] In this prospective study, which includes data from an interim analysis of an ongoing trial (NCT03366051), we hypothesized that the addition of lymphadenectomy to SLN mapping in endometrial cancer is related to higher morbidity and has a negative impact on QoL in comparison with SLN biopsy alone.

METHODS

The complications and lymphedema assessment, surveillance methods and statistical analysis are detailed in online supplemental file 1.

Patients

Between December 2017 and April 2022, patients with presumed early-stage endometrial cancer who underwent SLN mapping were prospectively recruited. We included patients with high-risk tumors from the ALICE trial (NCT03366051)—a multicentric open-label prospective randomized ongoing trial. The trial is assigning high-risk patients to undergo SLN mapping only or SLN mapping with systematic lymphadenectomy.[13]

Briefly, the ALICE trial is including patients with high-risk tumors, such as high-grade histology (endometrioid grade 3, serous, clear cell, and carcinosarcoma), endometrioid grades 1 or 2 with myometrial invasion of ≥50% or cervical invasion, clinically suitable to undergo systematic lymphadenectomy. For the present study we also included patients not suitable for ALICE trial and with low-risk tumors that only had SLN mapping.

Finally, patients were divided in two groups: SLN group (only SLN mapping) and SLN+LND group (SLN mapping with addition of lymphadenectomy). The study was approved by the institutions' review boards (#2441-17B) and all patients signed an informed consent. The data were collected, input, and managed using Research Electronic Data Capture software.[14]

Patient-reported Outcome

The first data were captured before surgery and during follow-up at 1, 6, and 12 months with the application of QoL questionnaires by the European Organization for Research and Treatment of Cervical Cancer Quality of Life Questionnaire 30 (EORTC-QLQ-C30) and EORTC-QLQ-Cx24. All the scales and single-item measure scores range from 0 to 100. The QoL scores were analyzed according to EORTC Scoring Manual.[15]

RESULTS

Patients' Demographics

The study's flowchart is depicted in Figure 1. Clinical and pathological data are summarized in Table 1.

The study included 152 patients, allocated in two groups: SLN group (n=113; 74.3%) and SLN+LND group (n=39; 25.7%). Indocyanine green was used in 84 (55.3%) cases and blue dye in 68 (44.7%). Only 14 (9.2%) cases had a unilateral detection, mostly in blue dye cases (n=10; p=0.035).

The median number of resected SLN (entire cohort) was 2,[1–7] and 18 (11.8%) cases had lymph node metastasis—6 (3.9%) macrometastasis, 10 (6.6%) micrometastasis, and 2 (1.3%) isolated tumor cells. Additionally, the median resected lymph nodes in the group SLN+LND was 22 (range 4–45), with median pelvic and para-aortic lymph nodes of 16 (range 4–31) and 10 (range 2–22), respectively.

There were no differences between the groups in age (p=0.15), BMI (p=0.62) and minimally invasive approach (p=0.82). However, the SLN+LND group had longer surgical time (mean, 274±65 vs 160±104 min; p<0.001) and intensive care unit use (23.1% vs 3.5%; p<0.001). Notably, 20 (13.1%) cases were considered American Society of Anesthesiologists (ASA) 3 patients, with higher rates in the SLN+LND group (25.6%) than in the SLN group (8.8%). (Table 1)

As anticipated, the groups differed with regard to pathologic features. Patients in the SLN+LND group were more likely to have non-endometrioid histologies (30.8% vs 11.5%; p=0.005), grade 3 tumors (81.6% vs 21.2%; p<0.001), deep myometrial invasion (41% vs 14.2%; p<0001), and presence of lymphovascular space invasion (38.5% vs 20.4%; p=0.02). Therefore, the SLN+LND group received more adjuvant treatment (87.2% vs 39.8%; p<0.001). (Table 1)

Intra-Operative and Early Complications (≤30 days)

Two (5.1%) patients had an intra-operative complication with obturator nerve injury (one thermal injury and one partial sectioning), and both belonged to the SLN+LND group (p=0.065). Early complications occurred in 29 (19.1%) cases. Patients who underwent SLN+LND had overall higher surgical complication rates than those who underwent only SLN (33.3% vs 14.2%; OR=3.03, 95% CI 1.29 to 7.09; p=0.009). Patients in the SLN group had grades 1, 2, and 3 complications in 10.6%, 2.6%, and 0.8%, respectively. Moreover, for SLN+LND group, complications grade 1, 2, 3 and 5 occurred in 17.9%, 10.2%, and 2.5% and 2.5%, respectively. Notably, grade ≥3 complications were uncommon in both groups (0.8% vs 5%; p=0.16).

Four patients had two or more types of complications: 1 (0.8%) in the SLN group and 3 (7.7%) patients in the SLN+LND group. The surgical complications are depicted in Table 2.

We also evaluated the impact of age, ASA, body mass index (BMI) and minimally invasive approach on the risk of post-operative complications. ASA 3 did not impact the risk of complication (OR=1.15, 95% CI 0.35 to 3.77; p=0.1), similarly for age (OR=0.98, 95% CI 0.93 to 1.03; p=0.50), BMI (OR=1.00, 95% CI 0.94 to 1.07; p=0.81), and minimally invasive approach (OR=0.33, 95% CI 0.10

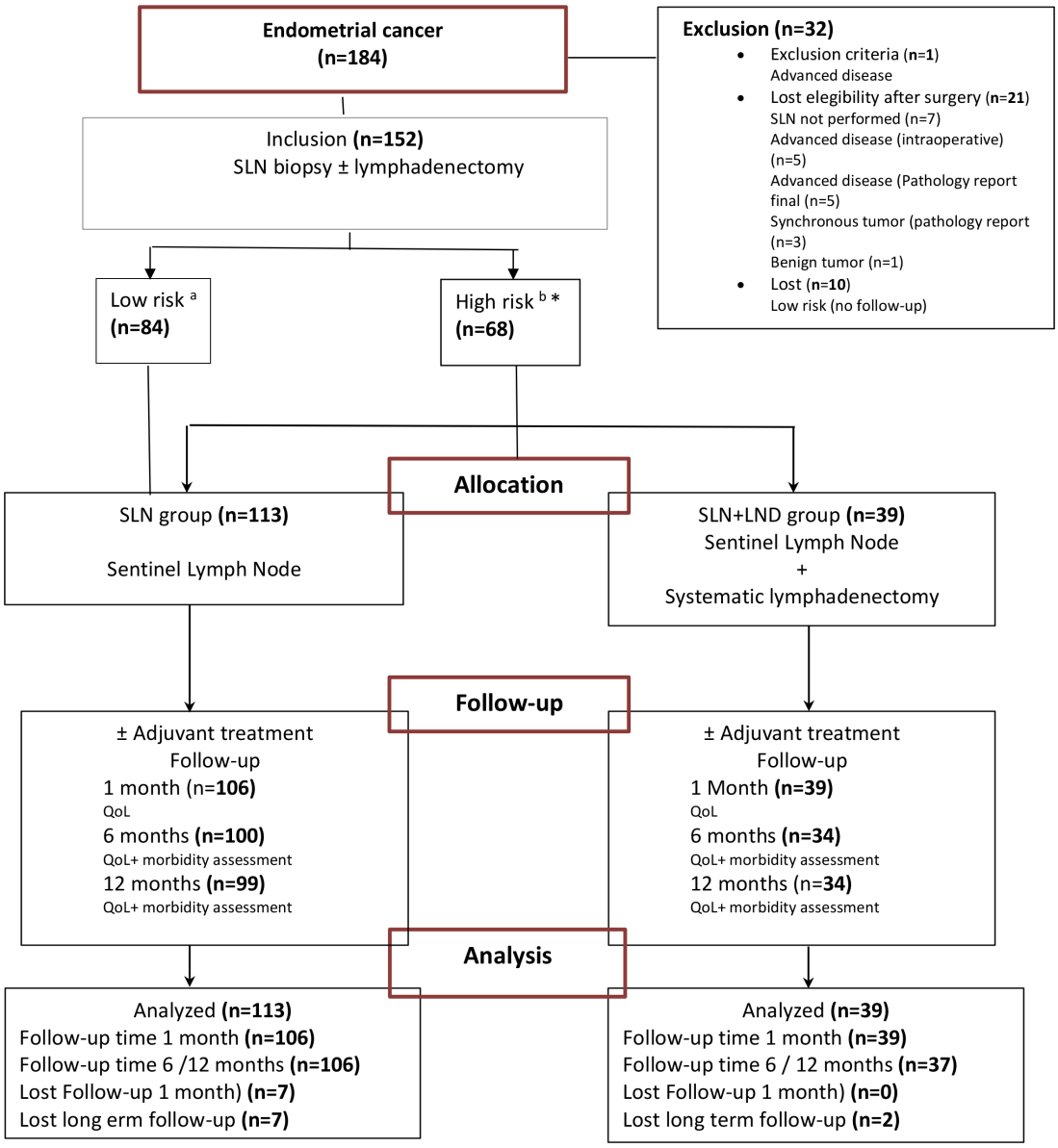

Figure 1 Study flowchart. SLN: Sentinel Lymph Node; LND: Lymphadenectomy; Qol: Quality of life. "Endometrioid G1/2 and myometrial invasion <50%. [b]Endometrioid G3,non-endometrioid and myometrial invasion 250%. *Patients from Alice Trial (NCT 03366051).

to 1.11; p=0.073). Moreover, the addition of lymphadenectomy (SLN+LND group) maintained as independent variable for the risk of complication after adjusting for surgical approach and ASA (OR=3.45, 95% CI 1.40 to 8.47; p=0.007).

Eight patients (5.3%) developed lymphocele with median post-operative time of 142 days (range 24–401). Notably, lymphocele occurred only in patients who underwent lymphadenectomy (p<0.001) and 3 (37.5%) cases were symptomatic—1 (12.5%) case underwent image guided drainage and 2 (25%) received intravenous antibiotics.

Lymphedema

Lymphedema was noted after clinical evaluation in 33 (24.4%) patients—84.8% (n=28) grade 1 and 15.2% (n=5) grade 2. Lymphedema after clinical examination was found in 21.2% of patients in the SLN group and 33.3% in the SLN+LND group at 12 months after surgery (p=0.14). We noted clinical grade 1 lymphedema for SLN and SLN+LND groups in 15.9% (n=18) and 25.6% (n=10) of cases, respectively. Moreover, grade 2 lymphedema for SLN and SLN+LND groups were 2.6% (n=3) and 5.1% (n=2), respectively. We did not record grade 3 lymphedema.

Notably, the increase difference volumes of ≥10% from 6 to 12 months did not differ between groups, being 23.2% (n=19/82) for SLN and 13.3% (n=4/30) for SLN+LND groups (p=0.38). Conversely, we found an association between clinical and lymphedema assessment reported by QoL questionnaire (p<0.001). The lymphedema score had the highest mean when lymphedema was reported by clinical examination at 6 months (30.1 vs 7.8; p<0.001) and at 12 months (36.3 vs 6.0; p<0.001). We found no association between

Table 1 Clinical and pathological characteristics of women undergoing primary surgery for endometrial cancer.

Characteristics	SLN (n=113) Mean (SD)	SLN+LND (n=39) Mean (SD)	Total (n=152) Mean (SD)	P value
Age	60.3 (8.0)	62.4 (6.0)	60.8 (7.5)	0.15
BMI	30.1 (6.5)	30.7 (5.9)	30.3 (6.4)	0.62
Surgical time length (min)	160 (65)	274 (104)	189 (91.5)	<0.001
	n (%)	n (%)		P value
ASA				<0.001
ASA 1	5 (4.4%)	8 (20.5%)	13 (8.5%)	
ASA 2	98 (86.7%)	21 (53.8%)	119 (78.3%)	
ASA 3	10 (8.8%)	10 (25.6%)	20 (13.2%)	
ICU				<0.001
No	109 (96.5%)	30 (76.9%)	139 (91.4%)	
Yes	4 (3.5%)	9 (23.1%)	13 (8.6%)	
ECOG*				0.68
0	90 (81.8%)	28 (75.7%)	118 (80.3%)	
1	17 (15.5%)	8 (21.6%)	25 (17.0%)	
2	3 (2.7%)	1 (2.7%)	4 (2.7%)	
Randomization				<0.001
No	80 (70.8%)	3 (7.7%)	83 (54.6%)	
Yes	33 (29.2%)	36 (92.3%)	69 (45.4%)	
Surgical approach				1.0
Laparotomy	10 (8.8%)	3 (7.7%)	13 (8.6%)	
MIS	103 (91.2%)	36 (92.3%)	139 (91.4%)	
Histological grade†				<0.001
1	57 (50.4%)	3 (7.9%)	60 (39.7%)	
2	32 (28.3%)	4 (10.5%)	36 (23.8%)	
3	24 (21.2%)	31 (81.6%)	55 (36.4%)	
Histological type				0.11
Endometrioid	100 (88.5%)	27 (69.2%)	127 (83.6%)	
Serous	4 (3.5%)	4 (10.3%)	8 (5.3%)	
Clear cell	1 (0.9%)	1 (2.6%)	2 (1.3%)	
Mixed	2 (1.8%)	2 (5.1%)	4 (2.6%)	
Carcinosarcoma	2 (1.8%)	3 (7.7%)	5 (3.3%)	
Dedifferentiated	4 (3.5%)	2 (5.1%)	6 (3.9%)	
Histological type				
Endometrioid	100 (88.5%)	27 (69.2%)	127 (83.6%)	0.005
Non-endometrioid	13 (11.5%)	12 (30.8%)	25 (16.4%)	
LVSI				0.02
Absent	90 (79.6%)	24 (61.5%)	114 (75%)	
Present	23 (20.4%)	15 (38.5%)	38 (25 %)	
Cervical stromal invasion				0.18
No	106 (93.8%)	34 (87.2%)	140 (92.1%)	
Yes	7 (6.2%)	5 (12.8%)	12 (7.9%)	
Myometrial invasion				<0.001
No invasion	20 (17.7%)	9 (23.1%)	29 (19.1%)	
<50%	77 (68.1%)	14 (35.9%)	91 (59.9%)	
≥50%	16 (14.2%)	16 (41%)	32 (21.1%)	

Continued

Table 1 Continued

Characteristics	SLN (n=113) Mean (SD)	SLN+LND (n=39) Mean (SD)	Total (n=152) Mean (SD)	P value
SLN metastasis	13 (11.5%)	5 (10.2%)	18 (11.8%)	0.92
ITC	2 (15.3%)	0	2 (11.1%)	
Micrometastasis	7 (53.8%)	3 (60%)	10 (55.5%)	
Macrometastasis	4 (30.7%)	2 (40%)	6 (33.4%)	
Adjuvant therapy				
No	68 (60.2%)	5 (12.8%)	73 (48%)	<0.001
Yes	45 (39.8%)	34 (87.2%)	79 (52%)	
Type of adjuvant therapy				0.60
Chemotherapy only	1 (2.2%)	1 (2.9%)	2 (2.5%)	
EBRT only	3 (6.7%)	2 (5.9%)	5 (6.3%)	
Chemotherapy+EBRT	4 (8.9%)	3 (8.8%)	7 (8.9%)	
VB only	12 (26.7%)	10 (29.4%)	22 (27.8%)	
EBRT+VB	9 (20%)	2 (5.9%)	11 (13.9%)	
Chemotherapy+VB	0 (0%)	1 (2.9%)	1 (1.3%)	
Chemotherapy+EBRT+VB	16 (35.6%)	15 (44.1%)	31 (39.2%)	

*Missing data in 5 cases (3 cases SLN and 2 SLN+LND).
†Missing data in 1 case (SLN+LND).
ASA, American Society of Anesthesiologists; BMI, body mass index; EBRT, external beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; ICU, intensive care unit; ITC, isolated tumor cells; LND, lymphadenectomy; LVSI, lymphovascular space invasion; MIS, minimally invasive surgery; SLN, sentinel lymph node biopsy; VB, vaginal brachytherapy.

adjuvant external beam radiotherapy and lymphedema (p=0.73).

Patient-Reported Outcome

The full function and symptoms scores from the study groups are depicted in online supplemental tables 1,2.

Function Scores

Although the graphics seem to show better global health status scores in favor of the SLN group during the follow-up, we could not find a statistically difference between groups. The social functioning score was most preserved at 1 month (means 83.4 vs 71.7; p=0.012) and 6 months (means 86.8

Table 2 Description of early surgical complications after sentinel node biopsy±lymphadenectomy.

Early surgical complications	SLN, n (%)	SLN+LND, n (%)	Total
Urinary tract infection	5 (17.2%)	0	5 (17.2%)
Surgical wound infection	4 (13.8%)	1 (3.4%)	5 (17.2%)
Seroma	2 (6.9%)	0	2 (6.9%)
Vaginal bleeding	3 (10.3%)	0	3 (10.3%)
Fecaloma	0	4 (13.8%)	4 (13.8%)
Sepsis	0	1 (3.4%)	1 (3.4%)
Abdominal wall hematoma	0	1 (3.4%)	1 (3.4%)
Neuropathic pain	0	2 (6.9%)	2 (6.9%)
Skin dehiscence	0	1 (3.4%)	1 (3.4%)
Lymphocele	0	2 (6.9%)	2 (6.9%)
Intense acute pain	1 (3.4%)	0	1 (3.4%)
Vascular complications	0	1 (3.4%)	1 (3.4%)
Drug allergy	1 (3.4%)	0	1 (3.4%)
Total	16 (55.2%)	13 (44.8%)	29 (100%)

SLN, sentinel lymph node biopsy; LND, lymphadenectomy.

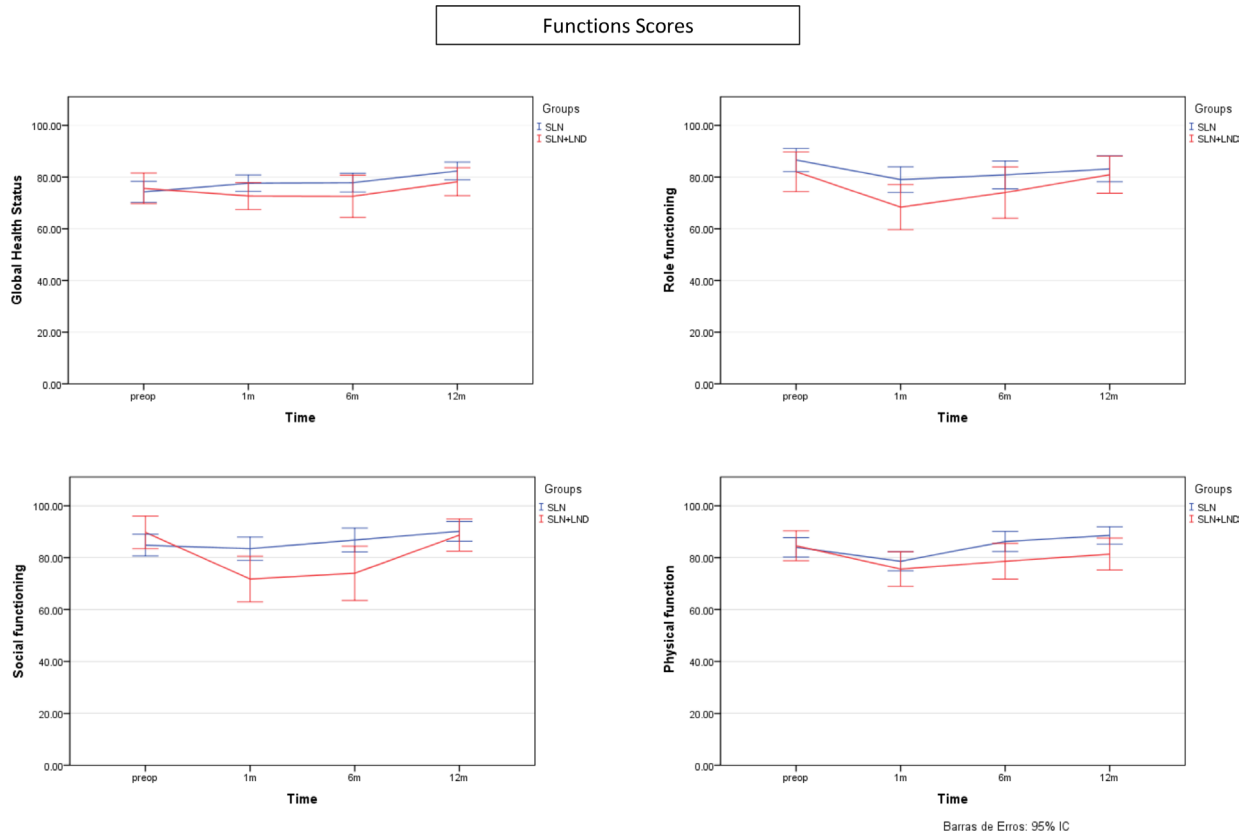

Figure 2 Graphical representation of mean functions scores during follow-up comparing SLN and SLN+LND groups: (A) global health status; (B) role functioning; (C) social functioning; (D) physical function.

vs 74.01; p=0.011) after surgery for the SLN group than for the SLN+LND group. Moreover, physical function scores were most preserved in the SLN group during follow-up and at 1 month (means, 78.3 vs 71.7; p=0.03) (Figure 2).

Symptom Scores

Patients in the SLN+LND group experienced greater symptoms related to lymphedema compared with SLN group at 12 months of follow-up (means 23.5 vs 12.4; p=0.022). Additionally, a better symptom experience score was recorded at 6 months and related to general symptoms for the SLN group compared with that for the SLN+LND group (means, 5.61 vs 9.38; p=0.047), however with no difference at 12 months (5.8 vs 8.3; p=0.17). (Figure 3)

DISCUSSION

Summary of Main Results

We performed an interim analysis for complication rates and QoL including patients from the ongoing ALICE trial and cases not suitable for the trial with addition of low-risk tumors, although with similar follow-up. We found that patients who underwent additional lymphadenectomy had increased early surgical morbidity and some decreased QoL scores recorded in function and symptoms questionnaires. Moreover, this is the first study that prospectively evaluated lymphedema and QoL comparing SLN mapping and SLN with addition of lymphadenectomy in endometrial cancer, and we noted a higher rate of lymphedema after lymphadenectomy.

Results in the Context of Published Literature

Early Complications

While the landscape of lymph node staging in endometrial cancer is shifting from systematic lymphadenectomy to SLN biopsy,[16] data comparing a complications' profile of the two methods are lacking. Dioun et al[17] retrospectively analyzed a large database (n=45 381), and SLN mapping was associated with a decreased risk of complications compared with lymphadenectomy (5.9% vs 7.3%; RR=0.85, 95% CI 0.77 to 0.95) after adjusting for confounders. Accorsi et al[6] recorded higher intra-operative (RR=14.25, 95% CI 1.85 to 19.63) and 30-day complication rates (RR=3.11, 95% CI 1.62 to 5.98) for women who underwent lymphadenectomy compared with SLN mapping. Conversely, Casarin et al[18] noted that SLN biopsy (n=188) had a shorter mean operative time, less blood loss compared with lymphadenectomy (n=198), but with no difference in complication rates. Notably, the three studies found that SLN mapping did not worsen morbidity compared with no lymph node staging.

In our study, patients who received additional systematic lymphadenectomy had overall more early complications compared with SLN mapping group. As the two groups were not similar in all clinical variables, we also performed an adjustment for possible confounding factors, and the addition of lymphadenectomy remained an independent risk for complications. Notably, most complications were low grade (grades 1 and 2), and therefore better captured in a prospective design.

For QoL, HORIZONS UK was a large (n=1222), single-arm study that included all gynecologic cancers and evaluated predictive

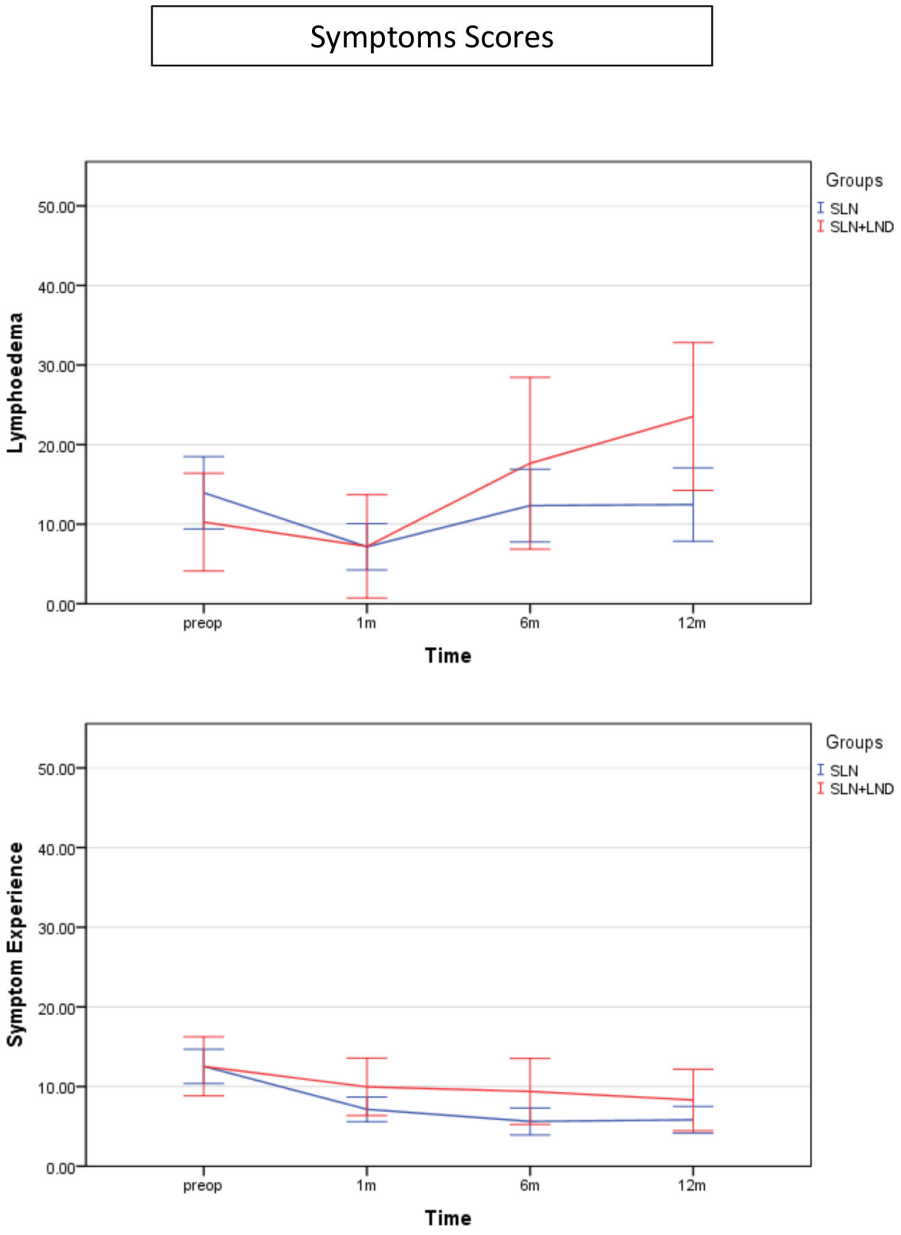

Figure 3 Graphical representation of mean symptom scores during follow-up comparing SLN and SLN+LND groups: (A) lymphedema; (B) symptom experience. LND, lymphadenectomy; SLN sentinel lymph node.

factors that affected a women's life at diagnosis and up to 12 months. The authors noted that QoL declined from baseline to 3 months, followed by an improvement at 12 months.[11] Our study aimed to compare two methods of node staging; we found some specific worse scores' outcomes for the SLN+LND group, reflecting the potential morbidity associated with lymphadenectomy. However, we found no statistically significant difference between groups for global health status score.

Lymphedema Assessment

We assessed the development of lymphedema by three different methods during 12 months of follow-up. The GOG 244 study suggested at least 2 years follow-up for lower limb lymphedema symptoms,[19] similar to a recent prospective study in cervical cancer that suggested lymphedema diagnosis after 15 months of surgery.[20] Additionally, Leitao et al published a large retrospective study that incorporated a patient-reported outcomes questionnaire in lymphedema and noted an increased lymphedema rate for patients after lymphadenectomy compared with only SLN (40.9% vs 27.2%; p=0.002).[9] The authors reported a long median follow-up time of 63.2 and 93.1 months for SLN and lymphadenectomy groups, respectively.

We found a clinical lymphedema rate of 33.3% in the SLN+LND group compared with 21.2% in the SLN group, which was not statistically significant and higher than expected for the SLN group compared with results from other studies. In the study by Geppert et al, lymphedema was reported for the SLN and lymphadenectomy groups in only 1.3% and 18.1% of cases, respectively.[21] Lower limb edema in women with endometrial cancer might have a multifactorial origin, such as weight gain, sedentarism, and hormonal changes, and we might argue whether other factors would lead to

lower-limb changes rather than the resection of pelvic SLNs. Moreover, most lymphedema were classified as grade 1.

Like the GOG 244 study,[19] we found no correlation between the clinical criteria and perimetry. A possible explanation is that the lower limb extremity (foot) swelling is not captured by perimetry during leg circumference measurement, and this leads to discordance between perimetry and clinical evaluation or reported symptoms. Nevertheless, methods for lymphedema diagnosis are still controversial,[20] and the evaluation of lower limbs only by volume may neglect the dynamic process of lower limb lymphedema development. Growing evidence supports patient-reported outcomes in surgical oncology research and it is currently accepted[22 23] for the morbidity symptom assessment.[24] Moreover, the correlation between patient-reported outcomes and clinical evaluation has been considered a standard practice with good reproducibility.[19] Yet, we noted a worse mean QoL score regarding lymphedema for SLN+LND at 12 months of follow-up compared with only SLN and a relation between the EORTC score for lymphedema and clinical evaluation.

Two other predictive factors for lymphedema should be considered. First, pelvic radiation has been suggested as an important risk factor for lymphedema.[9 25] However, we did not find a relation between post-operative pelvic radiation and lymphedema, which might be explained by our short follow-up time. Second, we should report that all patients in the SLN+LND group had the circumflex lymph nodes spared, a surgical approach that might prevent lower limb lymphedema in patients who undergo full pelvic lymphadenectomy.[26]

Strengths and weaknesses

The present series is the first that prospectively addressed morbidity and QoL for women who underwent SLN compared with SLN with back-up lymphadenectomy. Moreover, lymphedema was assessed by three methods and although including patients during the pandemic, we had a low evaluation loss. However, it should be noted that inherent and unadjusted confounding factors might always affect the results as not all patients were part of the ongoing randomized study, leading to heterogeneous groups for some clinical and uterine features.

Implications for practice and future research

The present study supports SLN biopsy as a staging method with lower surgical complication rate. Moreover, the early recognition of lower-limb lymphedema during the first 12 months of follow-up may be appropriate by clinical and patient-reported outcome rather than perimetry. Interestingly, we had a high rate of lymphedema even after SLN biopsy compared with previous reports and it may be explained by the complexity of lymphedema recognition and classification, as well as its multifactorial origin.

CONCLUSIONS

We found that the addition of lymphadenectomy to SLN biopsy significantly increased the early complication rates as well as leading to higher rates of lymphocele and lymphedema according to the symptom score. Better QoL scores were recorded for the SLN group in some specific function and symptoms questionnaires; however, no difference was found for overall QoL when SLN biopsy was compared with back-up lymphadenectomy.

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SUPPLEMENT 1

Complications and lymphedema assessment

Surgical complications were categorized by Clavien – Dindo classification (1) and evaluated in the first 30 days of follow-up. The lymphedema assessment was performed through clinical assessment (physical examination by the researcher or surgeon) and lower limb perimetry. Perimetry was performed by the same professional that measured the lower limbs´ diameter with a flexible tape, starting from the heel line with the floor, and superiorly every 10 cm with the patient naked and standing. Volumetry was calculated by truncated cone formula and considered altered after increase of 10% (2,3). Moreover, clinical examination consisted in edema evaluation, sensation of heaviness, characteristics of the skin, and clothes or shoes habit change. (4)

Severity of lymphedema was categorized according to the International Society of Lymphology reflecting clinical evaluation, inspection of lower limbs and patient report of symptoms. Briefly, stage I represents an early accumulation and regress with limb elevation. Pitting may occur. Stage II signifies that limb elevation alone rarely reduces tissue swelling and pitting is manifested. Stage III encompasses lymphostatic disease, with skin changes and absent pitting. (5)

Nevertheless, we considered weight gain as a confound factor for lymphedema diagnosis, where the increase in the Body Mass Index (BMI) increases measurements and consequently the volume of lower limbs. Therefore, the lower limb volume increase was not considered related to the weight gain when the Spearman correlation coefficient were -0.320 ($p < 0.001$) and -0.223 ($p = 0.011$) between right and left legs measured at 6 and 12 months.

Surveillance and telemonitoring

During COVID-19 pandemic, from March 2020 to June 2020, the patients´ follow-up were done remotely by telemonitoring. Total of 26 women had follow-up assessment

time at 1, 6, and 12 months by telemonitoring and succeeded in 23 (88.5%) of the cases . (6) After the favorable experience of telemonitoring, patients with a lack of appointments during pandemic, patients´ that did not meet the research follow-up visit window (±15 days) were evaluated by telemonitoring. A total of 37 (24.2%) QoL assessments were performed through telemonitoring and was mostly performed at 12 months follow-up (n=27; 17.6%).

With regard of lymphedema evaluation, we had a higher loss at 12 months, where 19 (12.4%) patients did not respond the QoL, and 66 patients (43.1%) did not undergo perimetry. We can rely this issue on the experience of QoL assessment by telemonitoring. Sixty-eight (44.7%) women did not have adjuvant treatment, leading to less frequent hospital visits and therefore less opportunity lower limbs perimetry measurement. Yet, loss of hospital follow-up was identified in 10 (6.5%) patients and only one patient did not have any QoL evaluation in postoperative follow-up.

Statistical analysis

Simple frequencies, mean, median and standard deviation of all variables were calculated. Associations between categorical variables were analyzed chi-square test and Fisher's test when appropriate. Continuous variables were analyzed using the t test for independent samples. When the normality assumption was violated, we used the nonparametric Mann-Whitney test. For correlation analysis between the BMI difference and volume difference, we used Spearman's s. QoL scores were analyzed following the EORTC manual (7,8) Logistic regression were used for risk assessment and factors of interest were adjusted in multivariate analysis, with odds ratio (OR) for relative risk for the outcome considering a 95% confidence interval (CI).

The volume of the perimetry was used the truncated cone formula to transform the measurements into volume. A 10% increase was used as a reference as the value of volume increase between the moments from the measurement of the volume of the limb considered in the evaluation of the pre-surgical moment.(9) The analyses were performed with SPSS 25.0.0.1 (IBM Corporation, 2019). For all tests, $p<0.05$ was significant.

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Table S1 - EORTC QLQ-C30 questionnaire scores over time according to lymphadenectomy group

Scale/Item		N	Mean	SD	P value
Global health status	SLN	112	74.25	±21.70	0.722
	SLN+LND	39	74.64	±18.27	
Global health status 1m	SLN	108	77.62	±16.65	0.109
	SLN+LND	39	72.64	±16.10	
Global health status 6m	SLN	100	77.83	±18.24	0.178
	SLN+LND	34	72.54	±23.43	
Global health_status 12m	SLN	100	82.33	±17.37	0.219
	SLN+LND	34	78.18	±15.49	
Physical functioning general	SLN	112	77.36	±16.39	0.558
	SLN+LND	39	79.09	±14.11	
Physical functioning _general 1m	SLN	108	78.34	±15.95	0.030
	SLN+LND	39	71.70	±16.82	
Physical functioning general 6m	SLN	100	82.26	±17.83	0.088
	SLN+LND	34	76.22	±17.14	
Physical functioning general 12m	SLN	100	85.03	±16.31	0.361
	SLN+LND	34	82.18	±13.52	
Physical functioning	SLN	112	83.98	±19.87	0.862
	SLN+LND	39	84.61	±17.71	
Physical functioning 1m	SLN	108	78.62	±19.25	0.412
	SLN+LND	39	76.61	±20.57	
Physical functioning 6m	SLN	100	86.26	±19.53	0.051
	SLN+LND	34	78.62	±19.67	
Physical functioning 12m	SLN	100	88.60	±17.01	0.036
	SLN+LND	34	81.37	±17.65	
Role functioning	SLN	112	86.60	±24.07	0.309
	SLN+LND	39	82.05	±23.68	
Role functioning 1m	SLN	108	79.01	±26.01	0.032
	SLN+LND	39	68.37	±26.98	
Role functioning 6m	SLN	100	80.83	±27.04	0.051
	SLN+LND	34	74.01	±28.48	
Role functioning 12m	SLN	100	83.16	±25.12	0.360
	SLN+LND	34	80.88	±20.56	
Emotional functioning	SLN	112	59.87	±27.61	0.304
	SLN+LND	39	65.09	±26.01	
Emotional functioning 1m	SLN	108	71.06	±23.91	0.157

	SLN+LND	39	64.52	±26.47	
Emotional functioning 6m	SLN	100	74.77	±25.44	0.880
	SLN+LND	34	74.01	±24.25	
Emotional functioning 12m	SLN	100	79.08	±25.38	0.987
	SLN+LND	34	79.00	±19.82	
Cognitive functioning	SLN	112	79.16	±25.65	0.981
	SLN+LND	39	79.05	±21.19	
Cognitive functioning 1m	SLN	108	87.03	±20.42	0.106
	SLN+LND	39	80.76	±21.12	
Cognitive functioning 6m	SLN	100	84.00	±21.95	0.254
	SLN+LND	34	78.92	±23.32	
Cognitive functioning 12m	SLN	100	84.66	±21.14	0.784
	SLN+LND	34	85.78	±18.41	
Social_functioning	SLN	112	84.82	±22.32	0.222
	SLN+LND	39	89.74	±19.35	
Social functioning 1m	SLN	108	83.48	±23.62	0.012
	SLN+LND	39	71.79	±27.07	
Social functioning 6m	SLN	100	86.83	±23.24	0.011
	SLN+LND	34	74.01	±29.92	
Social functioning 12m	SLN	100	90.16	±19.11	0.700
	SLN+LND	34	88.72	±17.75	
Symptom scales	SLN	112	13.85	±14.53	0.687
	SLN+LND	39	14.93	±14.10	
Symptom scales 1m	SLN	108	11.95	±12.41	0.012
	SLN+LND	39	18.13	±14.57	
Symptom scales 6m	SLN	100	11.69	±15.15	0.083
	SLN+LND	34	17.04	±16.12	
Symptom scales 12m	SLN	100	8.76	±9.88	0.124
	SLN+LND	34	11.91	±11.18	
Fatigue	SLN	112	17.80	±22.03	0.972
	SLN+LND	39	17.94	±19.68	
Fatigue 1m	SLN	108	19.44	±20.17	0.030
	SLN+LND	38	28.65	±27.29	
Fatigue 6m	SLN	100	16.66	±23.45	0.038
	SLN+LND	34	26.47	±23.69	
Fatigue 12m	SLN	100	11.66	±15.90	0.036
	SLN+LND	34	18.62	±18.29	
Nausea vomiting	SLN	112	4.46	±14.14	0.247
	SLN+LND	39	7.69	±17.03	
Nausea vomiting 1m	SLN	108	1.69	±6.42	0.056

	SLN+LND	39	5.12	±10.22	
Nausea vomiting 6m	SLN	100	4.50	±14.38	0.221
	SLN+LND	34	9.31	±20.99	
Nausea vomiting 12m	SLN	100	2.16	±8.42	0.050
	SLN+LND	34	8.33	±17.04	
Pain	SLN	112	19.94	±28.10	0.318
	SLN+LND	39	25.21	±28.83	
Pain 1m	SLN	108	19.90	±26.42	0.125
	SLN+LND	39	27.77	±29.69	
Pain 6m	SLN	100	15.83	±27.04	0.604
	SLN+LND	34	18.62	±26.51	
Pain 12m	SLN	100	15.50	±23.71	0.779
	SLN+LND	34	14.21	±20.56	
Dyspnoea	SLN	112	7.44	±18.82	0.854
	SLN+LND	39	6.83	±13.63	
Dyspnoea 1m	SLN	108	3.70	±13.92	0.826
	SLN+LND	39	4.27	±13.63	
Dyspnoea 6m	SLN	100	4.66	±14.99	0.347
	SLN+LND	34	7.84	±21.08	
Dyspnoea 12m	SLN	99	3.03	±10.74	0.698
	SLN+LND	34	3.92	±13.64	
Insomnia	SLN	112	29.46	±34.87	0.642
	SLN+LND	39	26.49	±32.87	
Insomnia 1m	SLN	108	22.53	±29.11	0.682
	SLN+LND	39	24.78	±30.31	
Insomnia 6m	SLN	99	23.23	±30.28	0.312
	SLN+LND	34	29.41	±31.53	
Insomnia 12m	SLN	98	18.36	±25.38	0.315
	SLN+LND	34	23.52	±26.62	
Appetite loss	SLN	111	8.40	±22.68	0.529
	SLN+LND	39	5.98	±12.95	
Appetite loss_1m	SLN	106	4.08	±15.73	0.541
	SLN+LND	39	5.98	±18.53	
Appetite loss_6m	SLN	100	4.66	±14.99	0.347
	SLN+LND	34	7.84	±21.80	
Appetite loss 12m	SLN	100	2.33	±8.54	0.143
	SLN+LND	34	5.88	±19.19	
Constipation	SLN	112	12.50	±23.72	0.651
	SLN+LND	39	14.52	±25.12	
Constipation 1m	SLN	108	5.55	±16.11	0.001

	SLN+LND	39	27.35	±34.93	
Constipation 6m	SLN	99	8.75	±22.63	0.109
	SLN+LND	34	16.66	±29.87	
Constipation 12m	SLN	99	8.41	±23.49	0.734
	SLN+LND	34	6.86	±21.36	
Diarrhoea	SLN	111	5.40	±17.13	0.815
	SLN+LND	38	6.14	±15.21	
Diarrhoea 1m	SLN	107	2.80	±15.26	0.971
	SLN+LND	37	2.70	±12.11	
Diarrhoea 6m	SLN	98	6.46	±17.68	0.292
	SLN+LND	34	11.76	±27.07	
Diarrhoea 12m	SLN	100	3.66	±12.44	0.198
	SLN+LND	35	7.61	±16.34	
Financial_difficulties	SLN	112	13.98	±28.17	0.951
	SLN+LND	39	13.67	±25.03	
Financial difficulties 1m	SLN	106	14.77	±27.63	0.651
	SLN+LND	39	17.09	±26.34	
Financial difficulties 6m	SLN	98	13.94	±33.13	0.847
	SLN+LND	34	12.74	±24.63	
Financial difficulties 12m	SLN	98	7.48	±18.86	0.647
	SLN+LND	34	5.88	±12.89	

SLN: sentinel lymph node biopsy; LND: lymphadenectomy.

Table S2 - EORTC QLQ-Cx24 questionnaire scores over time according to lymphadenectomy group

Scale/Item		N	Mean	SD	P value
Symptom scales	SLN	112	13.85	±14.53	0.687
	SLN+LND	39	14.93	±14.10	
Symptom scales 1m	SLN	108	11.95	±12.41	0.012
	SLN+LND	39	18.13	±14.57	
Symptom scales 6m	SLN	100	11.69	±15.15	0.083
	SLN+LND	34	17.04	±16.12	
Symptom scales 12m	SLN	100	8.76	±9.88	0.124
	SLN+LND	34	11.91	±11.18	
Symptom Experience	SLN	111	12.53	±11.41	0.996
	SLN+LND	39	12.53	±11.44	
Symptom Experience 1m	SLN	108	7.14	±8.10	0.096
	SLN+LND	38	9.96	±10.96	
Symptom Experience 6m	SLN	100	5.61	±8.54	0.047
	SLN+LND	34	9.38	±11.85	
Symptom Experience 12m	SLN	99	5.81	±8.42	0.174
	SLN+LND	34	8.30	±11.08	
Body Image	SLN	111	11.86	±21.33	0.137
	SLN+LND	39	6.55	±10.10	
Body Image 1m	SLN	108	10.08	±16.31	0.966
	SLN+LND	38	9.94	±21.26	
Body Image 6m	SLN	100	9.33	±18.66	0.123
	SLN+LND	34	16.01	±28.84	
Body Image 12m	SLN	99	8.19	±16.69	0.098
	SLN+LND	34	13.72	±16.81	
Lymphoedema	SLN	110	13.93	±24.05	0.389
	SLN+LND	39	10.25	±18.97	
Lymphoedema 1m	SLN	107	7.16	±15.20	0.989
	SLN+LND	37	7.20	±19.46	
Lymphoedema 6m	SLN	100	12.33	±23.04	0.291
	SLN+LND	34	17.64	±30.96	
Lymphoedema 12m	SLN	99	12.45	±23.12	0.022
	SLN+LND	34	23.52	±26.62	
Peripheral Neuropathy	SLN	109	9.48	±23.17	0.154
	SLN+LND	39	16.23	±30.46	

Peripheral Neuropathy 1m	SLN	106	5.34	±13.90	0.190
	SLN+LND	38	11.40	±26.02	
Peripheral Neuropathy 6m	SLN	99	14.81	±26.60	0.004
	SLN+LND	34	36.27	±37.93	
Peripheral Neuropathy 12m	SLN	97	13.74	±24.88	0.009
	SLN+LND	33	28.28	±33.45	
Menopausal Symptoms	SLN	110	25.75	±36.86	0.355
	SLN+LND	39	19.65	±30.31	
Menopausal Symptoms 1m	SLN	107	22.74	±33.83	0.113
	SLN+LND	38	13.15	±25.15	
Menopausal Symptoms 6m	SLN	98	29.59	±33.12	0.063
	SLN+LND	34	17.64	±28.70	
Menopausal Symptoms 12m	SLN	98	25.51	±32.03	0.074
	SLN+LND	34	14.70	±23.48	
Functional items	SLN	109	4.28	±14.59	0.540
	SLN+LND	39	5.98	±15.52	
Functional items 1m	SLN	102	2.28	±9.68	0.019
	SLN+LND	35	0.00	±0.00	
Functional items 6m	SLN	95	6.14	±15.95	0.652
	SLN+LND	33	7.57	±15.07	
Functional items 12m	SLN	96	13.36	±21.16	0.790
	SLN+LND	34	12.25	±20.22	
Sexual Vaginal baseline	SLN	17	12.25	±18.42	0.852
	SLN+LND	7	10.71	±14.20	
Sexual Vaginal 1m	SLN	11	6.06	±10.60	0.513
	SLN+LND	2	0.00	±0.00	
Sexual Vaginal 6m	SLN	18	31.01	±29.40	0.125
	SLN+LND	7	9.52	±12.19	
Sexual Vaginal 12m	SLN	32	22.13	±23.72	0.555
	SLN+LND	11	16.66	±19.36	
Sexual Worry	SLN	110	15.15	±28.78	0.290
	SLN+LND	39	10.25	±25.53	
Sexual Worry 1m	SLN	103	9.70	±21.20	0.243
	SLN+LND	34	5.88	±17.35	
Sexual Worry 6m	SLN	99	12.79	±27.64	0.633
	SLN+LND	34	14.70	±28.65	
Sexual Worry 12m	SLN	100	11.33	±24.26	0.590
	SLN+LND	34	14.70	±27.45	

Sexual Activity	SLN	109	4.28	±14.41	0.402
	SLN+LND	39	5.12	±12.18	
Sexual Activity 1m	SLN	101	1.65	±7.26	0.181
	SLN+LND	35	0.00	±0.00	
Sexual Activity 6m	SLN	95	6.66	±16.55	0.610
	SLN+LND	33	9.09	±20.87	
Sexual Activity 12m	SLN	96	13.54	±21.40	0.365
	SLN+LND	34	8.82	±14.92	
Sexual Enjoyment	SLN	15	31.11	±32.03	0.680
	SLN+LND	7	38.09	±35.63	
Sexual Enjoyment 1m	SLN	10	30.00	±29.18	0.545
	SLN+LND	1	0.00	±0.00	
Sexual Enjoyment 6m	SLN	17	27.45	±26.96	0.865
	SLN+LND	6	27.77	±13.60	
Sexual Enjoyment 12m	SLN	32	38.54	±25.55	0.401
	SLN+LND	11	48.48	±27.33	

SLN: sentinel lymph node biopsy; LND: lymphadenectomy.