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SENTIREC – The sentinel node mapping in women with cervical cancer study – Patient-reported early lymphedema and its impact on quality of life

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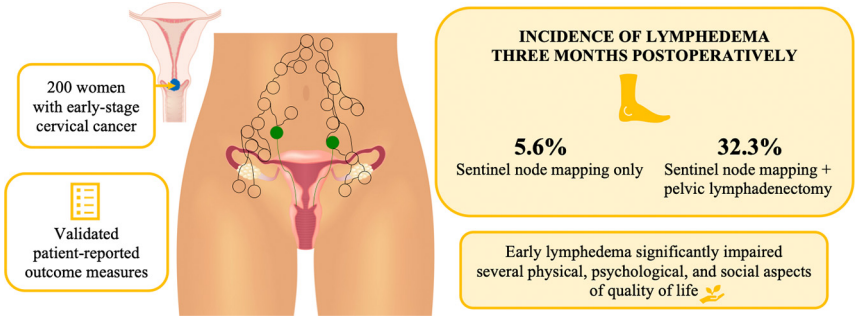
HIGHLIGHTS

- Sentinel node mapping only is associated with a low risk of self-reported lymphedema after surgery for cervical cancer.
- Sentinel node mapping combined with pelvic lymphadenectomy is associated with a high incidence of early lymphedema.
- Lymphedema symptoms after pelvic lymphadenectomy significantly impaired physical performance and appearance.
- Reporting early lymphedema is significantly associated with impairment in several quality of life domains and symptoms.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. To evaluate patient-reported incidence and severity of early lymphedema and its impact on quality of life (QoL) after sentinel lymph node (SLN) mapping only and after SLN and pelvic lymphadenectomy (PL) in women undergoing surgery for early-stage cervical cancer.

Methods. In a national prospective multicenter study, we included women with early-stage cervical cancer from March 2017–January 2021 to undergo radical surgery including SLN mapping. Women with tumors >20 mm underwent completion PL. The incidence and severity of early lymphedema and its influence on QoL

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were evaluated using validated patient-reported outcome measures before surgery and three months postoperative. We investigated changes over time using linear regression.

Results. Two hundred of 245 (81.6%) included women completed questionnaires at baseline and three months postoperatively. The incidence of early lymphedema was 5.6% (95% CI 2.1–11.8%) and 32.3% (95% CI 22.9–42.7%) in women who underwent SLN mapping only and SLN + PL, respectively. Lymphedema symptoms in the legs, genitals, and groins increased in both groups postoperatively but three times more in women who underwent PL. Lymphedema symptoms after SLN + PL significantly impaired physical performance ($p = 0.001$) and appearance ($p = 0.007$). Reporting lymphedema was significantly associated with impaired body image, physical-, role-, and social functioning, and a high level of fatigue.

Conclusions. SLN mapping alone carries a low risk of lymphedema in women undergoing surgery for early-stage cervical cancer. In contrast, completion PL is associated with a high incidence of early lymphedema. Reporting lymphedema is associated with significant impairment of several physical, psychological, and social aspects of QoL.

1. Introduction

Sentinel lymph node (SLN) mapping represents a less invasive staging procedure than radical pelvic lymphadenectomy (PL) and may reduce or prevent late effects as lymphedema [1–10]. Despite the increased implementation of SLN mapping, evidence on the potential reduction of lymphedema remains scarce [3,11,12]. Lymphedema has been associated with impaired quality of life (QoL) in women with gynecologic cancer, though data focusing on cervical cancer is lacking [13,14]. In the transition to SLN mapping, it is not only crucial to ascertain the accuracy of the technique but also to learn how the procedure affects women in terms of lymphedema. In this paper, we seek to contribute with this knowledge to improve future shared decision-making in nodal staging of women with early-stage cervical cancer.

The SLN mapping technique is gradually adopted in women with cervical cancer and low-risk disease (tumors ≤20 mm) due to the high sensitivity and negative predictive value (NPV) along with a well-documented low rate of nodal metastases [1,7,15–18]. Though recent studies have shown similar high sensitivity and NPV in women with large tumors (>20 mm), there is still an ongoing debate on the oncological safety in these women [7,19–21].

The most accurate method for detecting lymphedema has yet to be determined. Many studies have used limb circumferential measurement and ultrasound of subcutaneous tissue. However, these methods have limited validity due to daily individual changes [4]. Patient-reported outcome measures (PROMs) have proven useful in assessing lymphedema symptoms [9,10,22,23]. We initiated the national "SENTInel node mapping in women with CERvical cancer" (SENTIREC CERVIX) study with the overall purpose of evaluating SLN mapping in women with early-stage cervical cancer [7]. The current paper reports the incidence and severity of early lymphedema and its impact on QoL assessed by validated PROMs. The purpose is to evaluate 1) the incidence and severity of early lymphedema from baseline to three months postoperative in women who undergo SLN mapping only and in women who undergo SLN mapping with completion PL as part of their surgical treatment for early-stage cervical cancer, and 2) if the presence of early lymphedema affects the QoL in women with early-stage cervical cancer.

2. Methods

This national multicenter prospective cohort study on SLN mapping included women with FIGO-2009 IA2 with LVSI, IB1, IB2, or IIA1 cervical cancer consecutively from March 1, 2017, to January 8, 2021. Women with FIGO-2009 IA2-IB1 tumors ≤20 mm underwent SLN mapping alone, while women with FIGO-IB1 with tumor size >20 mm, IB2, and IIA1 underwent SLN mapping, radical PL, and systematic removal of FDG-PET/CT positive lymph nodes [7,24,25]. We refer to these two groups as SLN only and SLN + PL, respectively. We followed a SLN mapping algorithm with ultrastaging of all SLNs, removal of suspicious lymph nodes, and ipsilateral PL in cases where bilateral SLNs were not identified [7,26]. Therefore, some women in the SLN only group had more than SLNs removed. To reflect the clinical reality where bilateral SLN mapping is crucial for maintaining the safety of the procedure, these women remained in the SLN only group in the primary analyses.

The Regional Committees on Health Research Ethics for Southern Denmark (S-20150207) and the Data Protection Agency (15/52037) approved this study. The SENTIREC CERVIX trial was registered at clinicaltrials.gov (NCT02825355 and NCT02820506). All women provided written informed consent. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Odense Explorative Network (OPEN) [27,28].

2.1. Patient-reported outcome measures

Women completed electronic questionnaires preoperatively and three, 12, 24, and 36 months postoperatively. Women who were not able to complete questionnaires electronically received paper versions. This paper focuses on the baseline and three-month postoperative responses, thus reflecting the incidence and potential impact of early lymphedema on the patient's life.

To measure the incidence of early lymphedema, we used the European Organization for Research and Treatment of Cancer (EORTC) item library to select nine items on lymphedema (IL76) from the EORTC Vulva Cancer Module (QLQ-VU34). The QLQ-VU34 covers three domains on symptoms of lymphedema: leg, genital, and groin. SLN mapping in vulvar cancer resembles cervical cancer in terms of bilateral drainage and the prognostic importance of detecting nodal metastases [29,30].

The severity of lymphedema was measured using the validated Lymphedema Quality of Life Tool (LYMQOL) [31]. The LYMQOL is a condition-specific QoL measure for lymphedema of the legs, including 22 items in five domains; function, appearance, symptoms, emotion, and QoL. The function domain assesses how swelling affects daily activities, while the appearance domain evaluates how the swelling affects, e.g., the ability to find clothes that fits. The symptom domain covers pain, numbness, tingling, weakness, and heaviness, while the emotion domain assesses, e.g., trouble sleeping and tenseness. The QoL domain consists of one item on the overall QoL at present. We translated the LYMQOL questionnaire to Danish using independent forward-backward translation and pilot-tested the questionnaire [32]. Only women who responded positively to any of the nine items in the IL76 completed the LYMQOL.

We assessed QoL using the generic EORTC QLQ-C30 Core Module and the EORTC disease-specific Cervical Module (QLQ-CX24) [33–35]. All items were measured on a 4-point Likert scale of 'Not at all', 'A little', 'Quite a bit', and 'Very much'/'A lot' ('Very much' in EORTC items and 'A lot' in the LYMQOL), while the generic QoL item in the LYMQOL was measured on a 10-point Likert scale from poor to excellent and the global QoL scale on a 7-point scale in the EORTC QLQ-30.

2.2. Statistical methods

We compared demographics and patient characteristics between participants and non-participants using Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. Fisher's exact test was used in categorical variables with expected values under five.

To date, there is no consensus on the definition of lymphedema [23]. To evaluate the incidence of lymphedema and to assess change over time, it was necessary to set a cut-off for lymphedema. The hypothesized provisional scale structure of the IL76 as part of the EORTC QLQ VU34, includes three separate domains on leg lymphedema, groin lymphedema, and vulva swelling and is based on a preliminary matrix analyses and conceptual discussions within the EORTC gynecological collaboration group. We defined the incidence of lymphedema as any positive response ('A little', 'Quite a bit' or 'Very much') to at least six of nine items in the IL76. This cut-off took at least two of three domains of the IL76 into account and would take all three into account in most cases. It was decided to use this hypothesized scale structure, here as a sum score, but also to present data on the three domain scores (leg, groin, vulva). We used McNemar's test to evaluate the difference in the incidence of lymphedema from baseline to three months postoperatively in the SLN only and SLN + PL group. A *t*-test with unequal variance was used to evaluate the correlation between number of lymph nodes removed and the presence of lymphedema three months postoperatively.

We calculated mean scores and 95% confidence intervals (CI) for each domain and performed a linear transformation of the scores ranging from 0 to 100 according to the EORTC QLQ-C30 scoring manual [36]. The linear transformation was performed in all questionnaires for

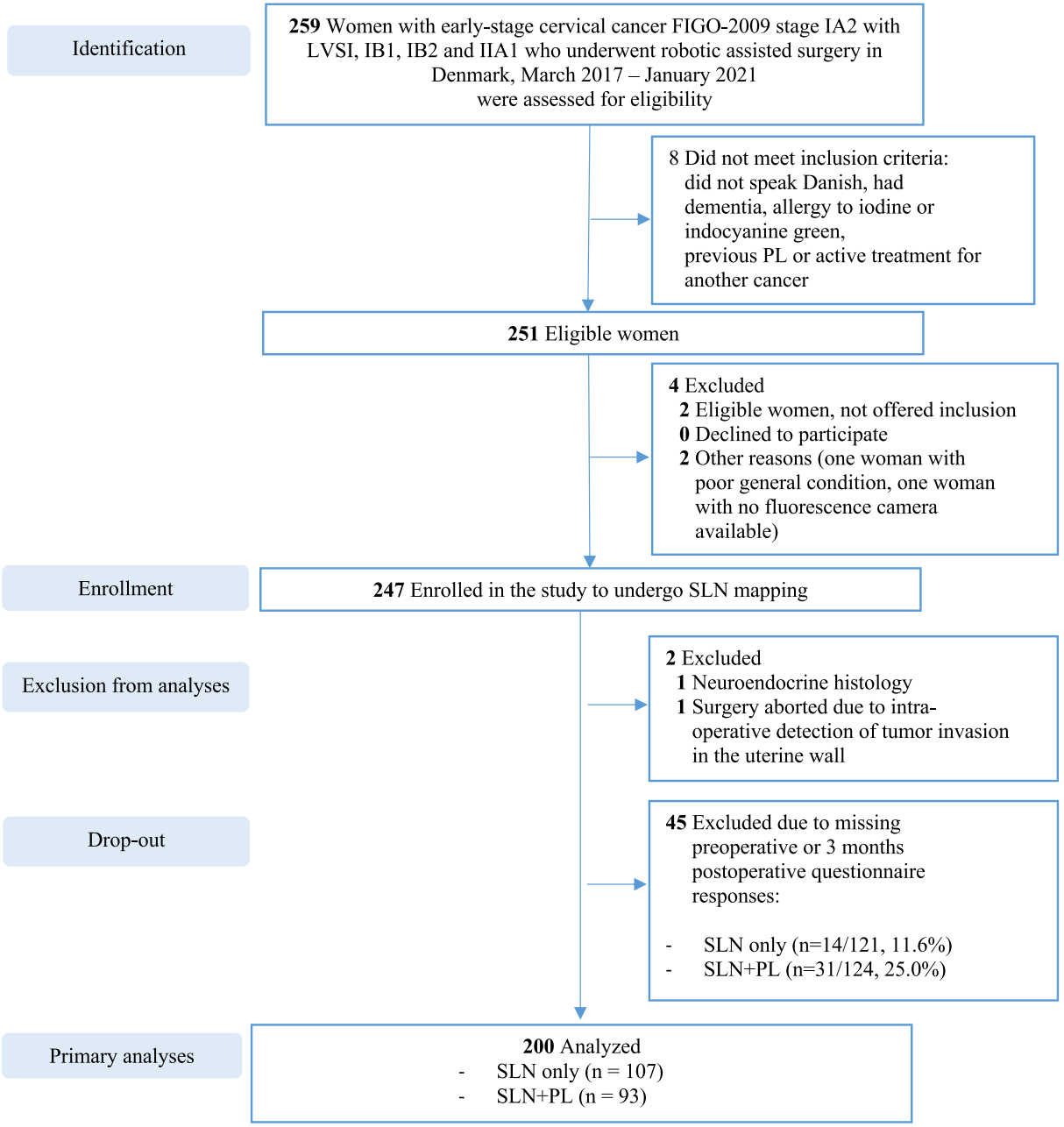


Fig. 1. The STROBE flowchart on inclusion of women in the SENTIREC CERVIX study.
Abbreviations: FIGO, the International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; SLN, sentinel lymph node; PL, pelvic lymphadenectomy.

comparison purposes since all questionnaires were rated on matching Likert scales. In function scales, the higher the domain score, the better the function. In symptom scales, high scores correspond to a high level of symptoms. Domain scores were set to missing if >50% of items in each domain were unanswered. A difference score from baseline to three months postoperative of 10 points on the transformed 100-point scale was considered clinically important in the IL76, LYMQOL, and EORTC QLQ-CX24. [37,38] In the EORTC QLQ-C30, we used the thresholds for clinical importance by Giesinger et al. to interpret baseline and three-month mean scores [39]. To interpret the change scores, we used the thresholds proposed by Cocks et al., allowing us to assess trivial, small, medium, and large minimal clinically important changes in each domain [40]. We evaluated the difference scores and the difference of differences using linear regression with robust variance estimation to account for the non-normality and variance heterogeneity. We performed an explorative analysis on the postoperative difference score between groups (SLN only and SLN + PL groups), adjusting for adjuvant therapy, age, BMI, and hemi- or full PL in cases of failed SLN mapping in the SLN only group. However, the SLN only and SLN + PL groups are inherently different due to a higher risk of lymph node metastases and adjuvant therapy in women with larger tumors (SLN + PL). Therefore, caution is advised in the interpretation of this analysis. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using STATA, version 16.0 (STATA Inc., Texas, USA).

3. Results

We included 245 of 251 eligible women (97.6%) (Fig. 1). The overall response rate of the baseline and three-month questionnaires was 81.6% (200/245). A total of 107 women underwent SLN only, and 93 women underwent SLN + PL. Of the 107 women who underwent SLN only, 16 underwent additional hemi- or full PL due to failed SLN mapping. Participants and non-participants differed in age, Charlson Comorbidity Index (CCI), smoking, adjuvant therapy, and site of hospital inclusion (Table 1).

3.1. The incidence of early lymphedema

Responses to the EORTC IL76 are presented in Fig. 2. The incidence of lymphedema increased from 0.0% (0/107) to 5.6% (6/107) three months postoperatively in women who underwent SLN only ($p = 0.01$). In the SLN + PL group, the incidence of lymphedema increased from 3.2% (3/93) to 32.3% (30/93) ($p < 0.001$). Excluding the women who underwent hemi- or full PL due to failed mapping, the incidence of lymphedema in women who underwent SLN only was 3.3% three months postoperatively ($p = 0.08$). Women with lymphedema three months postoperatively had significantly more lymph nodes removed than women without lymphedema (mean 23.4, 95% CI 19.4–27.5 vs. mean 13.4, 95% CI 12.4–16.3; $p < 0.001$).

The mean domain scores on symptoms of lymphedema are given in Table 2. Lymphedema symptoms in the legs, genitals, and groins

Table 1
Demographic and clinical characteristics of women in the SENTIREC CERVIX study.

	SLN only ($n = 107$)	SLN + PL ($n = 93$)	Participants ($n = 200$)	Non-participants[a] ($n = 45$)	
	Median (range)	Median (range)	Median (range)	Median (range)	P-value[b]
Age (years)	43 (26–84)	43 (26–80)	43 (26–84)	55 (28–79)	0.002
Body mass index (kg/m^2)	25 (18–46)	25 (18–43)	25 (18–46)	26 (19–41)	0.91
	n (%)	n (%)	n (%)	n (%)	P-value[c]
Inclusion hospital					
OUH	53 (49.5%)	48 (51.6%)	101 (50.5%)	8 (17.8%)	<0.001
CUH	39 (36.5%)	28 (30.1%)	67 (33.5%)	37 (82.2%)	
AUH	15 (14.0%)	17 (18.3%)	32 (16.0%)	0 (0.0%)	
Smoking					
Never smoker	61 (57.0%)	50 (53.8%)	111 (55.5%)	11 (24.4%)	0.001[d]
Previous smoker	25 (23.4%)	25 (26.9%)	50 (25.0%)	17 (37.8%)	
Smoker	19 (17.8%)	15 (16.1%)	34 (17.0%)	14 (31.1%)	
Unknown status	2 (1.9%)	3 (3.2%)	5 (2.5%)	3 (6.7%)	
CCI ≤ 1	105 (98.1%)	91 (97.9%)	196 (98.0%)	40 (88.9%)	0.01[d]
FIGO-2009					
IA1[e]	2 (1.9%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0.16[d]
IA2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IB1 ≤ 20 mm	94 (87.9%)	20 (21.5%)	114 (57.0%)	13 (28.9%)	
IB1 > 20 mm	10[f] (9.3%)	68 (73.1%)	78 (39.0%)	28 (62.2%)	
IB2	1 (0.9%)	5 (5.4%)	6 (3.0%)	4 (8.9%)	
Histology					
Squamous cell carcinoma	55 (51.4%)	59 (63.4%)	114 (57.0%)	32 (71.1%)	0.07[d]
Adenocarcinoma	47 (43.9%)	29 (31.2%)	76 (38.0%)	10 (22.2%)	
Adenosquamos carcinoma	3 (2.8%)	3 (3.2%)	6 (3.0%)	1 (2.2%)	
Clear cell carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	
Other[g]	2 (1.9%)	2 (2.2%)	4 (2.0%)	1 (2.2%)	
Lymph node metastases	7 (6.5%)	21 (22.6%)	28 (14.0%)	10 (22.2%)	0.17
Adjuvant therapy[h]	11 (10.3%)	44 (47.3%)	55 (27.5%)	22 (48.9%)	0.005

Abbreviations: SLN, Sentinel Lymph Node; PL, Pelvic lymphadenectomy; OUH, Odense University Hospital; CUH, Copenhagen University Hospital; AUH, Aarhus University Hospital; CCI, Charlson Comorbidity Index.

[a] Women who were excluded to missing baseline or 3 months postoperative questionnaires.
[b] Wilcoxon rank sum test.
[c] Chi-squared test.
[d] Fisher's exact test.
[e] Stage IA1 was not part of the inclusion criteria, these women were all included due to conization without free margins, with no residual tumor on final pathology.
[f] Reasons for not performing PL include comorbidities, tumor size 21–22 mm or the presence of high-risk or intermediate-risk factors with direct referral to adjuvant therapy.
[g] Glassy cell carcinoma (n = 1), Low differentiated carcinoma (n = 1), Primary mesonephric carcinoma (n = 1), Sarcomatoid planocellular carcinoma (n = 1), Serous carcinoma (n = 1).
[h] External beam radiation and concomitant chemotherapy.

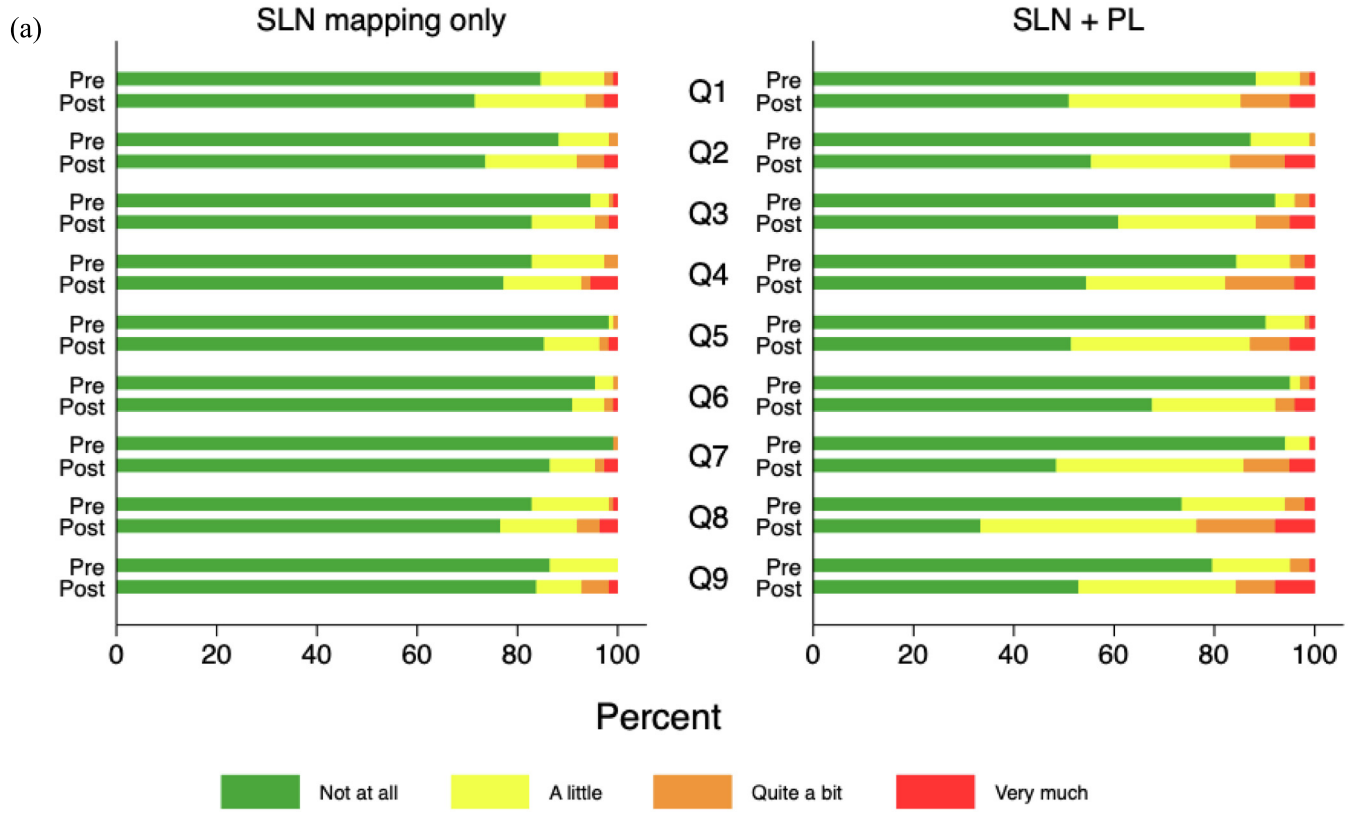
increased in both groups postoperatively but three times more in women who underwent SLN + PL. An explorative analysis showed that the postoperative difference scores between groups (SLN only compared to SLN + PL) differed significantly in multivariate analyses adjusting for adjuvant therapy, age, BMI, and hemi- or full PL in cases of failed SLN mapping in the SLN only group (difference in difference of the leg domain $p < 0.001$, genital domain $p = 0.002$), and groin domain $p = 0.004$).

3.2. The severity of early lymphedema

LYMQOL responses are shown in Table 3; only women who reported symptoms of lymphedema in the IL76 items responded to the LYMQOL questionnaire to indicate the severity and the impact on their lives. Both groups reported significant heaviness, weakness, and pain in the legs. However, women who underwent SLN + PL had more severe lymphedema as indicated by more impaired physical performance ($p = 0.001$) and appearance ($p = 0.007$), e.g., the ability to find shoes and clothes that fit (Table 3).

3.3. Quality of life in women with lymphedema

The effect of lymphedema on QoL was assessed by the EORTC QLQ-C30 and QLQ-CX24 questionnaires (Table 4). We compared women with ($n = 36$) and without lymphedema ($n = 164$) as defined by responses to the EORTC IL76. There was no significant difference in age (mean 41.0 vs. 43.5; $p = 0.05$), BMI (mean 24.7 vs. 25.0; $p = 0.65$), incidence of nodal metastases (6/36, 16.7% vs. 22/164, 13.4%; $p = 0.61$) or adjuvant therapy (12/36, 33.3% vs. 43/164, 26.2%; $p = 0.39$) between women with and without early lymphedema. There was a significant difference in the nodal staging procedure: a higher proportion of women who reported early lymphedema underwent SLN + PL (30/36, 83.3%) as compared to 16.7% (6/36) of women who underwent SLN only ($p < 0.001$). Early lymphedema was associated with significant



(b)
Q1: Have you had swelling in one or both legs?
Q2: Have you felt heaviness in one or both legs?
Q3: Has the skin felt tight in your leg(s)?
Q4: Have you had pain in your leg(s)?
Q5: Have you had swelling in the genital area?
Q6: Has the skin felt tight in your genital area?
Q7: Have you had swelling in your groin?
Q8: Have you had sore skin in your groin?
Q9: Have you had pain in your groin?

Fig. 2. The incidence of early lymphedema according to the EORTC IL76 questionnaire in women with early-stage cervical cancer.
Abbreviations: EORTC, European Organization of Research and Treatment of Cancer; IL76, Item Library 76; SLN, Sentinel Lymph Node; PL, Pelvic lymphadenectomy; Pre, preoperative scores; Post, postoperative scores.
(a) Crude proportions of responses to the EORTC IL76 questionnaire.
(b) Questions in the EORTC IL76.

Table 2
Domain scores on the incidence of early lymphedema according to the EORTC IL76 in women with early-stage cervical cancer.

	SLN only	SLN+PL
Leg	(n=106)	(n=93)
Baseline, mean score (CI)	5.0 (2.9;7.2)	5.6 (2.9;8.4)
Three months postoperative, mean score (CI)	10.9 (7.1;14.7)	21.2 (16.1;26.4)
Difference	5.9 (2.1;9.7)	15.6 (10.9;20.2)
P-value[a]	0.002	<0.001
Genital	(n=104)	(n=92)
Baseline, mean score (CI)	1.1 (-0.3;2.5)	4.0 (1.0;7.0)
Three months postoperative, mean score (CI)	5.6 (2.5;8.7)	18.5 (13.3;23.7)
Difference	4.5 (1.1;7.9)	14.5 (9.0;20.0)
P-value[a]	0.01	<0.001
Groin	(n=107)	(n=93)
Baseline, mean score (CI)	3.6 (1.8;5.5)	7.9 (4.7;11.1)
Three months postoperative, mean score (CI)	9.1 (5.5;12.8)	26.6 (21.2;32.0)
Difference	5.5 (1.5;9.5)	18.7 (12.8;24.6)
P-value[a]	0.007	<0.001

Abbreviations: EORTC, European Organization of Research and Treatment of Cancer; IL76, Item Library 76; SLN, Sentinel Lymph Node; PL, Pelvic lymphadenectomy; CI, Confidence Interval.
Leg, Genital and Groin domain scores are symptom scales, i.e., high domain-scores correspond to a high level of symptoms.
[a] Linear regression with robust variance estimation.
Grey coloring: Difference over clinically important threshold of 10 on a 0–100 scale.

impairment regarding body image ($p = 0.002$), global health status ($p = 0.04$), physical- ($p = 0.008$), role- ($p = 0.04$), cognitive- ($p = 0.04$), and social functioning ($p = 0.007$), as well as a higher level of fatigue ($p = 0.01$), pain ($p = 0.04$), dyspnea ($p = 0.03$), and symptom experience ($p = 0.007$) (Table 4).

In women with early lymphedema, the mean scores exceeded the thresholds for clinical importance postoperatively with impairment of physical-, role-, emotional-, and cognitive functioning, as well as fatigue, nausea and vomiting, pain, dyspnea, and diarrhea (Table 4). Further, early lymphedema resulted in a large minimal clinically important deterioration of fatigue and role functioning postoperatively and a medium deterioration in physical-, cognitive- and social functioning, in addition to pain, dyspnea, and constipation. In the EORTC QLQ-CX24, both groups reported clinically important differences exceeding the threshold with impairment of sexual functioning and sexual worry. However, difference scores were larger in women reporting lymphedema.

4. Discussion

Our study contributes with new and comprehensive knowledge regarding early lymphedema in women with early-stage cervical cancer. Using repeated measures, we show that women who undergo SLN mapping only rarely develop early lymphedema, while women who undergo SLN + PL have a higher incidence and more severe early lymphedema. Eighteen percent of women developed early lymphedema, which negatively impacted several aspects of their QoL; physically, psycho-socially, and sexually. Our evaluation included several validated PROMs and updated guidelines regarding PRO analyses and interpretation. The majority of women with early-stage cervical cancer are comparatively young [41]. Therefore, it is crucial to prevent excessive treatment and detrimental lymphedema in these women. We have earlier reported that in women with tumors ≤20 mm, the SLN mapping technique has a very high detection rate and a low risk of metastases [7]. The present data confirm that the SLN procedure in itself carries a low risk of lymphedema. The incidence of early lymphedema and its impact on QoL should be considered along with accuracy and oncological safety data regarding SLN mapping, even in women with tumor size >20 mm [7]. Results from this study may be valuable in future guidelines regarding nodal staging procedures and shared decision in women with early-stage cervical cancer.

Prospective studies examining PRO assessed lymphedema have reported an incidence of lymphedema ranging from 14% to 46% in women undergoing PL [10,23,42–45]. Although it should be interpreted with caution due to our study design, the exploratory analyses comparing the two groups showed that PL seems to be predictive for early lymphedema. It has been questioned when and whether lymphedema develops early or late after PL. In a recent systematic review, 17 studies were excluded if they evaluated the incidence of lymphedema ≤6 months post-treatment. Here we show, that substantial lymphedema has already developed three months postoperatively, primarily in women undergoing completion PL after SLN. In the SENTICOL study, although using non-validated ad hoc questions, SLN + PL was associated with more severe leg heaviness and fatigue than SLN only [11]. In comparison, the SENTICOL study reported non-significant reduced top-thigh and mid-thigh limb circumferential measurements in the SLN only group, although this measure is likely to be influenced by day-to-day variations and inter-observatory differences. Further, in a retrospective study, physician-rated lymphedema was reported in 0.0% of the 70 women who underwent SLN only compared to 13.4% in 97 women who underwent PL [12]. In another small retrospective study, physician-rated lymphedema was described in 8.7% representing 23 women after SLN only, compared to 42.0% in 12 women who underwent completion PL due to identification of nodal metastasis [3]. Updated longitudinal results from the SENTIREC study will provide comprehensive knowledge on the course of lymphedema following SLN only and SLN + PL. The present three months data provides valuable and new evidence for patient information and communication.

Our results demonstrate a considerable deterioration of QoL in women who reported early lymphedema, involving several areas of psycho-social well-being and physical functioning. This data contributes

Table 3
Domain scores on the severity of early lymphedema according to the LYMQOL questionnaire in women with early-stage cervical cancer (only women who responded positively to any questions of the IL76 completed the LYMQOL).

	SLN only	SLN+PL
Function[a]	(n=36)	(n=36)
Baseline, mean score (CI)	94.4 (91.2;97.7)	93.2 (88.5;97.9)
Three months postoperative, mean score (CI)	90.0 (85.1;94.9)	78.1 (70.2;86.1)
Difference	-4.4 (-9.5;0.7)	-15.0 (-23.2;-6.9)
P-value[b]	0.09	<0.001
Appearance[a]	(n=36)	(n=35)
Baseline, mean score (CI)	91.7 (86.0;97.4)	92.5 (86.8;98.2)
Three months postoperative, mean score (CI)	86.6 (79.3;94.0)	82.0 (73.1;91.0)
Difference	-5.0 (-12.8;2.8)	-10.5 (-17.8;-3.1)
P-value[b]	0.20	0.007
Symptom[a]	(n=35)	(n=35)
Baseline, mean score (CI)	8.2 (4.3;12.0)	9.1 (4.0;14.3)
Three months postoperative, mean score (CI)	16.5 (9.7;23.3)	25.5 (17.1;33.9)
Difference	8.3 (1.3;15.4)	16.4 (8.2;24.6)
P-value[b]	0.02	<0.001
Emotion[a]	(n=29)	(n=34)
Baseline, mean score (CI)	60.9 (52.9;69.0)	63.1 (56.1;70.0)
Three months postoperative, mean score (CI)	72.4 (63.2;81.6)	64.5 (55.0;74.1)
Difference	11.5 (3.8<;19.2)	1.5 (-6.3;9.2)
P-value[b]	0.005	0.70
Quality of life[a]	(n=33)	(n=35)
Baseline, mean score (CI)	64.6 (54.1;75.2)	68.6 (58.1;79.0)
Three months postoperative, mean score (CI)	60.9 (48.6;73.3)	60.3 (49.9;70.8)
Difference	-3.7 (-16.3;8.9)	-8.3 (-19.1;2.6)
P-value[b]	0.55	0.13

Abbreviations: LYMQOL, Lymphedema Quality of Life Tool SLN, Sentinel Lymph Node; PL, Pelvic lymphadenectomy; CI, Confidence Interval.
[a] The function, appearance, emotion and Quality of Life domains are function scales, i.e., the higher the domain-score, the better the functions. A negative difference score is an impairment in functioning. The symptom domain is a symptom scale, i.e., high domain-scores correspond to a high level of symptoms. A positive difference score is a higher level of symptoms.
[b] Linear regression with robust variance estimation.
Grey coloring: Difference over clinically important threshold of 10 on a 0–100 scale.

to a better understanding of how women who develop early lymphedema after surgery for cervical cancer are affected in their everyday life. For example, women with lymphedema reported more difficulty with social-, physical-, role- and cognitive well-being. In other words, early lymphedema was associated with negative impairment of their daily life, including social relationships with friends and family, and led to difficulty completing work tasks and hobbies. Even everyday tasks of walking, getting dressed, and putting on shoes were significantly impaired. In addition, women with early lymphedema reported increased symptoms of pain and fatigue. Responses further revealed that several aspects of sexuality were more severely impaired in women with early lymphedema, e.g., body image including feelings of being less attractive and feminine, sexual enjoyment, sexual functioning, and sexual worry. Our results highlight the importance of providing sufficient evidence for the least invasive surgical treatment without compromising survival but also to focus on postoperative surveillance interventions regarding lymphedema.

Our findings are in agreement with the results by Beesley et al. [13], who conducted a population-based cross-sectional survey of 802 gynecological cancer survivors, including 197 women with cervical cancer, in 2004. The survey demonstrated higher relative odds of psychological, physical, and sexual needs in women diagnosed with lymphedema. In addition, a large proportion of the women with lymphedema reported a need for information, prevention, treatment, and assistance with pain or discomfort in the legs. Recently, Carter et al. [14] published a study assessing the impact of PRO-assessed lymphedema on QoL after gynecologic surgery. The Gynecologic Cancer Lymphedema Questionnaire (GCLQ) was used to define the diagnosis of lymphedema, while QoL was evaluated by the Functional Assessment of Cancer Therapy (FACT) questionnaire at baseline, six, 12, 18, and 24 months after surgery. Of 768 included women, 44.0% reported lymphedema between baseline and 24 months postoperatively which significantly impaired QoL ($p < 0.001$), body image ($p < 0.001$), sexual and vaginal function ($p < 0.001$), limb function ($p < 0.001$), and cancer distress ($p < 0.001$).

Carter et al. [14] performed a subgroup analysis of 115 women with early-stage cervical cancer. Women with lymphedema had significantly impaired sexual and vaginal functioning ($p < 0.04$) compared to women without lymphedema, while all other QoL domains showed non-significant differences. These results differ from ours, where several aspects of QoL were significantly impaired. Though our results show a minimal clinically important difference between groups in sexual and vaginal functioning, the difference was not significant ($p = 0.40$). The study design by Carter et al. [14] is very similar to ours, with PRO assessed lymphedema and QoL. Yet, comparison is difficult due to the difference in PROMs used to evaluate lymphedema and QoL. Further, Carter et al. did not report specific data for the cervical cancer group.

Table 4
The impact of early lymphedema on the quality of life in women with early-stage cervical cancer evaluated by the EORTC QLQ-C30 and QLQ-CX24 questionnaires.

	Women with lymphedema (n=36)			Women without lymphedema (n=164)			Difference between women with and without lymphedema	
	Baseline Mean (95% CI)	3 months postop. Mean (95% CI)	Difference[b] Mean (95% CI)	Baseline Mean (95% CI)	3 months postop. Mean (95% CI)	Difference[b] Mean (95% CI)	Mean (95% CI)	P-value[c]
QLQ-C30 Function[a]								
Physical functioning	91 (85;96)	77 (71;83)	-14 (-20;-7)	94 (92;96)	90 (88;92)	-4 (-6;-2)	-9 (-16;-2)	0.008
Global health status	59 (52;66)	51 (44;59)	-7 (-17;2)	71 (68;74)	74 (71;77)	3 (-1;6)	-10 (-20;-0)	0.04
Role functioning	77 (66;89)	52 (41;63)	-25 (-40;-10)	88 (84;91)	79 (75;83)	-9 (-14;-4)	-16 (-31;-1)	0.04
Emotional functioning	56 (48;63)	59 (51;68)	3 (-6;13)	68 (65;71)	79 (76;83)	11 (8;15)	-8 (-18;2)	0.11
Cognitive functioning	72 (64;79)	60 (50;70)	-12 (-22;-2)	82 (78;85)	81 (77;84)	-1 (-4;2)	-11 (-21;-1)	0.04
Social functioning	83 (75;92)	65 (54;75)	-18 (-29;-7)	91 (88;93)	88 (85;91)	-3 (-6;0)	-15 (-26;-4)	0.007
QLQ-C30 Symptom[a]								
Fatigue	34 (26;42)	54 (45;63)	20 (11;28)	24 (21;28)	32 (28;35)	7 (3;11)	12 (3;22)	0.01
Nausea and vomiting	9 (3;15)	16 (7;24)	7 (-1;15)	3 (2;5)	6 (4;8)	3 (0;5)	4 (-4;12)	0.32
Pain	25 (16;33)	42 (33;51)	17 (8;26)	12 (9;14)	19 (16;22)	7 (3;11)	10 (0;19)	0.04
Dyspnea	3 (-0;6)	18 (9;27)	15 (6;25)	7 (4;10)	12 (8;15)	5 (1;8)	11 (1;20)	0.03
Insomnia	35 (26;45)	36 (24;48)	1 (-14;16)	29 (24;33)	22 (18;26)	-6 (-11;-2)	7 (-7;22)	0.32
Appetite loss	19 (10;29)	27 (15;38)	7 (-5;18)	10 (7;13)	10 (7;13)	1 (-3;4)	6 (-6;18)	0.32
Constipation	11 (4;19)	36 (24;48)	23 (11;34)	6 (4;9)	18 (14;22)	11 (7;15)	11 (-0;23)	0.06
Diarrhea	12 (6;18)	19 (9;30)	7 (-4;17)	8 (6;11)	11 (7;14)	2 (-2;6)	4 (-7;15)	0.43
Financial difficulties	19 (8;31)	17 (7;28)	-3 (-10;5)	7 (5;10)	6 (4;9)	-1 (-4;2)	-2 (-10;6)	0.65
QLQ-CX24 Function[a]								
Body image	72 (62;81)	50 (39;60)	-22 (-33;-11)	84 (80;87)	79 (75;83)	-4 (-8;-1)	-18 (-29;-6)	0.002
Sexual activity	87 (78;96)	80 (73;87)	-7 (-16;2)	84 (81;88)	77 (73;81)	-8 (-12;-4)	1 (-8;11)	0.80
Sexual enjoyment	33 (12;54)	54 (39;69)	19 (-20;58)	21 (13;28)	41 (35;47)	12 (2;23)	7 (-25;39)	0.67
Sexual/vaginal functioning	88 (82;93)	61 (49;73)	-27 (-61;6)	93 (90;96)	74 (69;79)	-16 (-21;-11)	-11 (-38;15)	0.40
QLQ-CX24 Symptom[a]								
Symptom experience	16 (12;20)	23 (18;27)	6 (2;11)	12 (10;13)	12 (10;13)	0 (-1;2)	6 (2;11)	0.007
Lymphoedema	6 (-0;13)	45 (34;55)	38 (26;50)	6 (3;8)	11 (8;15)	5 (2;8)	33 (21;45)	<0.001
Peripheral neuropathy	13 (6;20)	22 (12;32)	9 (-2;19)	6 (3;8)	10 (7;14)	4 (1;8)	4 (-6;15)	0.44
Menopausal symptoms	18 (10;25)	30 (20;41)	13 (6;21)	13 (10;17)	20 (15;25)	6 (2;11)	7 (-2;15)	0.11
Sexual worry	41 (27;55)	75 (65;85)	33 (19;47)	25 (20;30)	46 (41;52)	21 (15;26)	13 (-2;27)	0.08

Abbreviations: EORTC, European Organization of Research and Treatment of Cancer; QLQ-C30, Quality of life Questionnaire Core Module; QLQ-CX24, Quality of life Questionnaire Cervical Module; Postop, postoperative; CI, Confidence Interval.
[a] In functional scales, high domain-scores correspond to a better function, and in symptom scales, high domain-scores correspond to a high level of symptoms. A negative difference in difference. Implies an impairment in function scales and a positive difference in difference implies a higher level of symptoms in symptom scales.
[b] Difference score between 3 months follow-up and baseline.
[c] Linear regression with robust variance estimation.
Thresholds of clinical importance: defined by Giesinger in the QLQ-30 (excluding global health status) and defined as a difference of 10 on a 0–100 scale in the CX24.
Cocks' thresholds of clinically important diferences (only applicable on QLQ-C30): green: trivial change; yellow: small change; orange: medium change; red: large change.

Hence, there is no information on the surgical modality and nodal staging procedure, as well as the incidence of lymphedema and QoL scores.

Using several different analytical approaches of PRO data, we provided evidence that reporting early lymphedema is associated with a negative impact on several aspects of the patient's quality of life. The use of PRO data allows individual subjective evaluation and promotes patient-centered care. However, it can be challenging to translate results of PRO data into a clinical setting due to the lack of internationally agreed guidelines regarding, e.g., the definition of minimal clinically important differences and thresholds for impairment in functioning and symptoms. Many methods of evaluating meaningful changes have been used, e.g., a difference score of 10 on a scale from 0 to 100 by Osoba et al. and a standard deviation of 0.5 by Norman et al. [37,46]. However, these methods do not necessarily take differences between questionnaires and domains into account. Recently, Giesinger et al. determined new thresholds of clinical importance for the EORTC QLQ-C30 by analyzing responses along with a questionnaire including anchor items on clinical significance [39]. These thresholds allow determining minimal clinical importance in scores obtained at a single point in time. Similarly, Cocks et al. developed thresholds of clinically relevant change for the EORTC QLQ-C30 by combining meta-analytic techniques with blinded expert opinions, allowing clinicians to better interpret significant changes over time. We applied these new methods of interpreting minimal clinical importance when assessing the impact of self-reported lymphedema on the woman's QoL. By analyzing difference scores and the difference of differences using linear regression, we accounted for preoperative symptomatology and impaired functioning. For example, by applying the Giesinger thresholds, we found that emotional functioning was affected at baseline in women with and without lymphedema, most likely due to their recent cancer diagnosis. Both groups of women showed improved emotional functioning postoperatively, but it was more pronounced in women without lymphedema. The Cocks thresholds of clinically important differences revealed that many areas of QoL were affected in women with early lymphedema, though especially fatigue and role functioning showed a large deterioration. Using the new methods of interpretation of the EORTC QLQ-C30, we illustrated a more nuanced impression of the extent and severity of impact that early lymphedema may have on a woman's QoL. This might allow clinicians to better decide on treatment options in patients with particularly impaired functioning and symptoms.

4.1. Strengths and limitations

The prospective national inclusion and the use of several validated PROMs with an updated analytical approach strengthened this study. Our study yielded a high participation rate (97.6%) and high compliance with the completion of questionnaires (81.6%).

Limitations to the study include possible confounding by indication due to our study design. Women with tumors >20 mm have a higher risk of metastases and are therefore more likely to undergo adjuvant therapy. Women who underwent SLN only are therefore inherently different from women who underwent SLN + PL. To account for this, we mainly interpreted repeated measure results. We did perform an additional explorative multivariate analysis between groups (SLN only compared to SLN + PL) to account for adjuvant treatment. However, we

advise caution in interpreting the multivariate analysis due to the inherent differences between groups.

Further, reporting early lymphedema and lower QoL could be attributable to bias related to the patient's knowledge regarding larger tumors, undergoing completion PL, nodal metastatic disease, and undergoing adjuvant therapy. However, there was no significant difference in nodal metastatic disease and adjuvant therapy between women with and without early lymphedema. The comparatively small proportion of women with early lymphedema did not allow adjusted multivariate analyses.

With no consensus on how to most validly assess lymphedema, our cut-off on lymphedema may have given an over- or underestimation. Further, we noted the significant differences between participants and non-participants. Non-participants were women who failed to respond to either baseline or three-month questionnaires. Non-participants were older, had a higher CCI, and were more likely to have undergone adjuvant therapy. Therefore, results may not be representative of the whole group of women with early-stage cervical cancer. Finally, only women with symptoms of lymphedema responded to the LYMQOL questionnaire. The small sample size in LYMQOL responses limited the interpretation of *p*-values and the ability to adjust for adjuvant therapy, age, and BMI.

5. Conclusion

Women who underwent SLN only as part of their surgical treatment for early-stage cervical cancer have a low risk of lymphedema. In contrast, women who undergo SLN + PL have a high incidence of lymphedema, which is associated with a severe impact on their physical performance and appearance three months postoperatively. Early lymphedema is associated with a significant impairment of several aspects of QoL. Results from this study may guide treatment decisions in future nodal staging approaches in women with early-stage cervical cancer.

Declaration of Competing Interest

There are no conflicts of interest to disclose.

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