GYNECOLOGY

Longitudinal effects of adjuvant chemotherapy and lymph node staging on patient-reported outcomes in endometrial cancer survivors: a prospective cohort study

David Forsse, MD; Mark L. Barbero, MD; Henrica M. J. Werner, PhD; Kathrine Woie, PhD; Nina Nordskar, MD; Elisabeth Berge Nilsen, MD; Marie Ellstrøm Engh, PhD; Ingvild Vistad, PhD; Astri Rege, MD; Margaret Sævik-Lode, MD; Stine Andreasen, MD; Ingfrid S. Haldorsen, PhD; Jone Trovik, PhD; Camilla Krakstad, PhD

BACKGROUND: Most patients with endometrial cancer with localized disease are effectively treated and survive for a long time. The primary treatment is hysterectomy, to which surgical staging procedures may be added to assess the need for adjuvant therapy. Longitudinal data on patient-reported outcomes comparing different levels of primary treatment are lacking, especially when adjuvant radiotherapy is omitted.

OBJECTIVE: We assessed the impact of lymphadenectomy and adjuvant chemotherapy on patient-reported symptoms, function, and quality of life. We hypothesized that these treatment modalities would substantially affect patient-reported outcomes at follow-up.

STUDY DESIGN: We prospectively included patients with endometrial cancer enrolled in the ongoing MoMaTEC2 study (ClinicalTrials.gov Identifier: NCT02543710). Patients were asked to complete the patient-reported outcome questionnaires European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EN24 preoperatively and at 1 and 2 years of follow-up. Functional domains and symptoms were analyzed for the whole cohort and by treatment received. To assess the effect of the individual treatment modifications, we used mixed regression models.

RESULTS: Baseline data were available for 448 patients. Of these patients, 339 and 219 had reached 1-year follow-up and 2-year follow-up, respectively. Treatment included hysterectomy (plus bilateral salpingo-oophorectomy) alone (n=177), hysterectomy and lymph node staging without adjuvant therapy (n=133), or adjuvant chemotherapy irrespective of staging procedure (n=138). Overall, patients reported improved global health status and quality of life (+9 units; $P<.001$), increased emotional and social functioning, and increased sexual interest and activity ($P<.001$ for all) from baseline to year 1, and these outcomes remained stable at year 2. Means of functional scales and quality of life were similar to age- and sex-weighted reference cohorts. Mean tingling and numbness and lymphedema increased after treatment. The group who received adjuvant chemotherapy had a larger mean reduction in physical functioning (−6 vs +2; $P=.002$) at year 1, more neuropathy (+30 vs +5; $P<.001$; year 1) at years 1 and 2, and more lymphedema at year 1 (+11 vs +2; $P=.007$) than the group treated with hysterectomy and salpingo-oophorectomy only. In patients not receiving adjuvant chemotherapy, patient-reported outcomes were similar regardless of lymph node staging procedures. Adjuvant chemotherapy independently increased fatigue, lymphedema, and neuropathy in mixed regression models.

CONCLUSION: Patients with endometrial cancer receiving adjuvant chemotherapy reported significantly reduced functioning and more symptoms up to 2 years after treatment. For patients treated by surgery alone, surgical staging did not seem to affect the quality of life or symptoms to a measurable degree at follow-up. Therefore, subjecting patients to lymph node removal to tailor adjuvant therapy seems justified from the patient's viewpoint; however, efforts should increase to find alternatives to traditional chemotherapy.

Key words: emotional functioning, laparotomy, lymphadenectomy, minimally invasive surgery, physical functioning, quality of life, sentinel node biopsy

Introduction

Endometrial cancer is the sixth most common cancer in women, with a lifetime risk reaching 2% to 3% in many industrialized countries.[1] Surgery is the cornerstone of treatment, consisting of hysterectomy and bilateral salpingo-oophorectomy, with the addition of lymph node staging (LNS) to assess the extent of spread and adjuvant radiation or chemotherapy for patients at a high risk of recurrence.[2] With an excellent 5-year survival at >90% for localized disease, treatment-related complications and posttreatment health-related quality of life (HRQoL) are gaining attention. Patient-reported outcome (PRO) data regarding these issues are limited but suggest benefits for minimally invasive surgery over laparotomy,[3,4] sentinel node biopsy over lymphadenectomy,[5,6] and potential long-term gastrointestinal symptoms for patients undergoing adjuvant radiotherapy.[7–9] Little is known about the effects of adjuvant chemotherapy on survivors of endometrial cancer, in particular beyond the initial treatment period. Many institutions, especially in the Nordic countries, have discontinued the use of adjuvant radiotherapy in favor of chemotherapy, based on data suggesting equal or better survival,[10–12] and the possibility of reserving radiotherapy for

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AJOG at a Glance

Why was this study conducted?

Longitudinal data on treatment-related patient-reported outcomes (PROs) in endometrial cancer are limited, especially regarding the role of lymph node staging (LNS) and adjuvant chemotherapy.

Key findings

Patients undergoing adjuvant chemotherapy expressed worse physical functioning and higher symptom burden, including tingling and numbness, lymphedema, and fatigue than patients not undergoing chemotherapy. Patients undergoing LNS without receiving adjuvant therapy did not differ in PROs from patients undergoing hysterectomy alone.

What does this add to what is known?

Although the risk of lymphedema with lymphadenectomy is established, this connection was not demonstrated in this large study with prospectively registered PROs and may be overrated in modern treatment algorithms. In contrast, adjuvant chemotherapy had clear detrimental effects, supporting a further stratification to reduce the number of patients needing chemotherapy, by surgical staging, novel biomarkers, or expanding the therapeutic arsenal.

salvage treatment. PRO data for patients undergoing these types of treatment algorithms may help identify and quantify treatment-related problems and contribute to better information to patients and prioritization of clinical efforts and research but are not yet available.

We evaluated prospectively registered PROs in treatment groups defined by the Norwegian national guidelines for the treatment of endometrial cancer, comprising selective lymphadenectomy or sentinel node biopsy and adjuvant chemotherapy for high-risk cases. We hypothesized that undergoing lymphadenectomy and/or adjuvant chemotherapy would have significant health effects that could be detected by self-reported outcome measurements.

Methods

Ethical considerations

The study has been approved according to the Norwegian legislation by the Western Regional Committee for medical and health research ethics (REK2015/0548). All patients included in the study gave written informed consent.

Patient series

MoMaTEC2 is an ongoing international multicenter phase 4 study (ClinicalTrials.gov Identifier: NCT02543710) for the implementation of preoperative assessment of hormone receptors as biomarkers to guide treatment in endometrial cancer. PROs are collected as secondary endpoints. All patients treated at Norwegian participating centers undergoing hysterectomy between October 15, 2015, and November 11, 2020, were eligible for this study. Clinicopathological characteristics and treatment information were collected at baseline. Patients with advanced disease (not completely resected at primary treatment) and patients receiving adjuvant treatment other than chemotherapy or additional second-line treatment because of recurrence were excluded (Figure 1). Treatment details for included patients are listed in Table 1, and treatment principles are outlined in detail in Appendix A.

A separate consent for PRO follow-up was obtained at inclusion, with 467 patients consenting to participate (participation rate at 71%). PRO respondents and nonrespondents had largely similar clinical profiles (Supplemental Table 1).

The patients included in the study were grouped on the basis of treatment received: hysterectomy and bilateral salpingo-oophorectomy (BSO) alone (Hyst group), hysterectomy with BSO and LNS (LNS group), and hysterectomy and BSO with adjuvant chemotherapy, with or without LNS (Chemo group) (Figure 1).

Patient-reported outcome

The general European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3 and endometrial cancer–specific EORTC QLQ-EN24 questionnaires were completed preoperatively (baseline) and annually after treatment. These questionnaires are validated to describe different and complementing dimensions of function and symptoms for patients with endometrial cancer and are available in Norwegian.[13,14] Norwegian reference data from EORTC QLQ-C30 were extracted from a previous survey in an unselected Norwegian population and adjusted by age and gender to reflect the study cohort.[15]

Function and symptom scales were derived according to the EORTC scoring manual[16] for scales that were considered relevant for our patient group. For functional scales, a positive change signified improved function. For symptomatic scales, a positive change signifies an increased amount of symptoms, that is, a deterioration. Response rates for most analyzed scales were found to be consistently high (97%–100%) at each time point (Supplemental Table 2). Exceptions were sexual interest and sexual activity with response rates of 93% and 94%, respectively, at baseline.

To evaluate the clinical impact of changes for EORTC scales, Cohen d was used to represent effect size, defined as the change in means divided by the pooled standard deviation.[17] We established cutoffs for our cohort by using the standard deviation of baseline values. Changes were interpreted according to Cohen general criteria as follows: trivial <0.2; small, 0.2–0.5; moderate, 0.5–0.8; and large, >0.8. These values are arbitrary; however, the 0.5 cutoff has been shown to be valid as a surrogate for a clinically relevant difference in HRQoL assessment.[18] We compared these effect sizes to previously published anchor-based cutoffs[19] and found little deviation (Supplemental Table 3).

To explore the development of relevant symptoms over time, a case-wise analysis of the EORTC QLQ-EN24 items regarding lymphedema and neuropathy (tingling and numbness) was performed in patients with completed 2 years follow-up. For this purpose, item responses were dichotomized into "no and light symptoms" ("none" or "a little") and "moderate and severe symptoms" ("quite a bit" or "very much"). For lymphedema, the most severe of the 2 corresponding item responses was selected.

Statistical analysis

All statistical analyses were performed in R (version 4.0.2; R Core Team 2020; R Foundation for Statistical Computing, Vienna Austria).

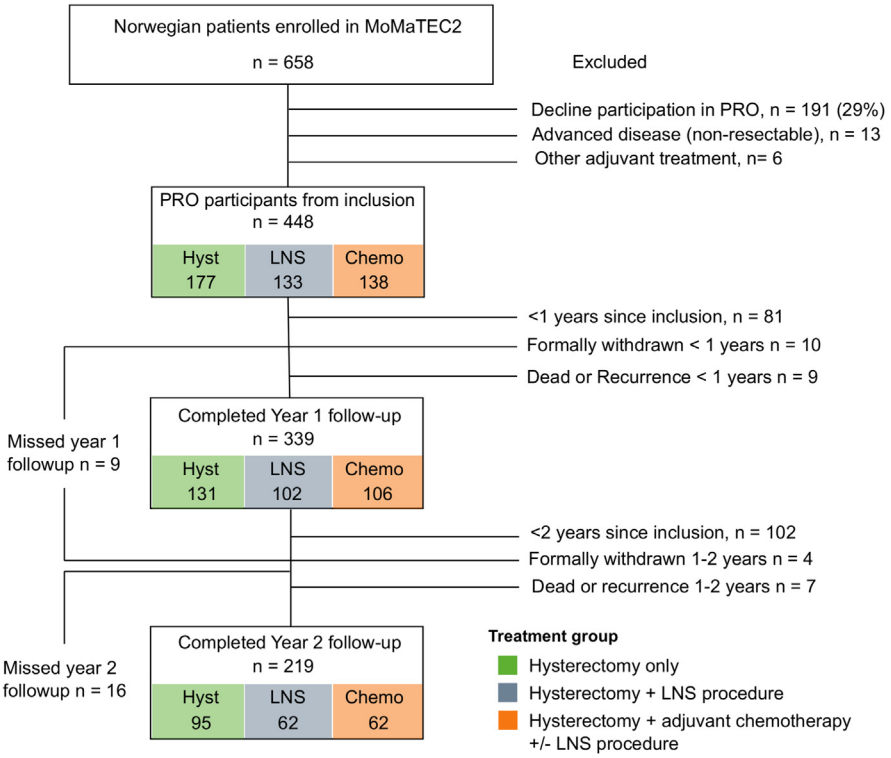
Missing entries were analyzed for nonrandomness using the R package "finalfit." Imputation was performed according to the EORTC scoring manual to compute scales despite missing items if <50% of relevant items were missing.[16] Missing scale scores occurred at low frequency (Supplemental Table 2) and were dropped without further imputation. This resulted in complete case analysis for statistical analyses comparing year to year changes except for linear mixed models, which can handle missing at random data points in longitudinal analysis through maximum likelihood modeling.

Categorical variables were compared by chi-square test or the Fischer exact test where appropriate, and differences in distributions of continuous variables were assessed by Mann-Whitney test for 2 groups or Kruskal-Wallis test for multiple group comparisons.

To assess changes in PRO scales over time for the entire cohort, Wilcoxon signed-rank test was used to compare changes in means from baseline to years 1 and 2. To assess differences between treatment groups at specific time points, the Mann-Whitney test was used. For these analyses, only cases with data for the time point of interest were included.

To explore how different treatment modalities independently affected PROs, effect magnitudes of EORTC scale changes were assessed, as described by the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium.[20] For each scale, a linear mixed model (R packages "lme4" and "lmerTest") was fitted with the scale score as a dependent variable, a subject-level random intercept, time and treatment factors as independent variables, and a baseline score covariate. Included treatment effects were surgical modality (laparoscopy or laparotomy), any LNS procedure, including sentinel node biopsy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy, and adjuvant chemotherapy (yes or no). Interaction terms between time and LNS and time and adjuvant chemotherapy were included to account for differences between years 1 and 2 of follow-up. In addition, separate models were explored where patients who underwent sentinel node biopsy with the removal of ≤4 nodes were grouped with patients without any lymph node sampling. Effect estimates (regression coefficients) with 95% confidence intervals (CIs) and *P* values were reported for all mixed models. *P* values of <.05 were considered statistically significant in all analyses.

FIGURE 1
Flow diagram of patient inclusion



LNS, lymph node staging; *PRO*, patient-reported outcomes.

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Results

At baseline, 448 patients had consented to participate in the PRO follow-up, of which 339 and 219 patients had reached follow-up at year 1 and year 2, respectively (Figure 1). LNS had been performed in 56% of participating patients, and 32% of participants had received adjuvant chemotherapy (Table 1). The treatment groups had similar age and body mass index (BMI) distribution but differed in treatment and histopathologic characteristics (Table 1). Patients in the Chemo group more often had undergone laparotomy (69% compared

TABLE 1
Clinical and pathologic characteristics of patients included in the study

Variable	Hyst group	LNS group	Chemo group	*P* value
Included (n)	176	132	138	
Age at treatment, median (IQR)	67 (14)	66 (13)	69 (11)	.129
Body mass index, median (IQR)	28.3 (8)	28.3 (7)	27.4 (7)	.219
	n (%)	n (%)	n (%)	*P* value
Mode of surgery (hysterectomy)				<.001
Laparotomy	16 (9)	40 (32)	88 (69)	
Robot-assisted laparoscopy	64 (37)	82 (66)	37 (29)	
Conventional laparoscopy	91 (53)	2 (2)	3 (2)	
LNS				<.001
Not performed	177 (100)	0 (0)	20 (14)	
Sentinel node mapping	0 (0)	34 (26)	17 (12)	
Pelvic lymphadenectomy	0 (0)	86 (65)	47 (34)	
Para-aortic and pelvic	0 (0)	13 (10)	54 (39)	
Lymph node metastasis				<.001
Not investigated	177 (100)	0 (0)	20 (14)	
Positive	0 (0)	0 (0)	30 (22)	
Negative	0 (0)	133 (100)	88 (64)	
FIGO stage				<.001
I	172 (98)	133 (100)	72 (52)	
II	3 (2)	0 (0)	22 (16)	
III	1 (1)	0 (0)	40 (29)	
IV	0 (0)	0 (0)	4 (3)	
Histologic group				<.001
EEC grade 1	110 (65)	72 (54)	12 (9)	
EEC grade 2	50 (29)	52 (39)	26 (19)	
EEC grade 3	5 (3)	5 (4)	32 (23)	
Nonendometrioid	5 (3)	4 (3)	68 (49)	
Recurrence within 2 y				.039
Yes	5 (3)	6 (5)	13 (9)	
No	172 (97)	127 (95)	125 (91)	

Data are presented as number (percentage) or median (IQR).

Chemo group, patients hysterectomy with adjuvant chemotherapy, with or without LNS; *EEC*, endometrioid endometrial cancer; *FIGO*, International Federation of Gynecology and Obstetrics; *Hyst group*, patients receiving hysterectomy alone; *IQR*, interquartile range; *LNS*, lymph node staging; *LNS group*, patients receiving hysterectomy with LNS procedure.

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with 32% in the LNS group and 9% in the Hyst group; $P<.001$) (Table 1). Among patients in the Chemo group, 39% had undergone a para-aortic dissection compared with 10% in the LNS group. Only 14% of the Chemo group had not undergone any LNS. The Chemo group had a significantly higher stage as defined by International Federation of Gynecology and Obstetrics (FIGO) system and more aggressive histologic subtypes ($P<.001$ for both). The rate of recurrences at 2 years was higher in the Chemo group (9.4% vs 4.5% and 2.8% for the LNS and Hyst groups; $P=.039$).

Patient-reported functioning

In the overall cohort, global health status and quality of life (QoL) increased from baseline to year 1 (+9 units; $P<.001$) and remained stable at year 2 (Table 2). Emotional function increased moderately from a mean score of 75 to 87 at year 1 and was stable at year 2 ($P<.001$).

TABLE 2
Overall cohort changes in EORTC scale means over time

		Baseline	Year 1			Year 2		
Functional scales[b]	Reference[a]	Mean (SD)	Mean (SD)	Effect size	*P* value[c]	Mean (SD)	Effect size	*P* value[d]
Global health status or QoL	72	69 (22)	78 (20)	Small	<.001[e]	76 (23)	Small	.002[e]
Physical function	80	87 (17)	86 (16)	Trivial	.279	85 (19)	Trivial	.115
Emotional function	83	75 (21)	87 (18)	Moderate	<.001[e]	86 (18)	Moderate	<.001[e]
Cognitive function	85	86 (19)	87 (18)	Trivial	.686	86 (19)	Trivial	.282
Social function	85	82 (22)	89 (20)	Small	<.001[e]	88 (21)	Small	.011[e]
Sexual interest	—	13 (22)	19 (26)	Small	<.001[e]	20 (25)	Small	<.001[e]
Sexual activity	—	9 (19)	15 (24)	Small	<.001[e]	14 (23)	Small	<.001[e]
Sexual enjoyment	—	65 (22)	57 (28)	Small	.514	55 (27)	Small	.303
Symptomatic scales[f]								
Fatigue	29	26 (23)	24 (23)	Trivial	.162	25 (26)	Trivial	.862
Lymphoedema	—	10 (18)	15 (22)	Small	<.001[e]	14 (20)	Small	.003[e]
Urologic symptoms	—	17 (19)	16 (18)	Trivial	.715	15 (16)	Trivial	.606
Gastrointestinal symptoms	—	16 (16)	14 (15)	Trivial	.232	14 (15)	Trivial	.503
Poor body image	—	9 (18)	8 (16)	Trivial	.211	9 (19)	Trivial	.655
Sexual and vaginal problems	—	16 (21)	20 (21)	Small	.124	24 (24)	Small	.054
Pain in the back and pelvis	—	27 (29)	23 (28)	Trivial	.014[e]	23 (29)	Trivial	.132
Tingling and numbness	—	11 (22)	24 (30)	Moderate	<.001[e]	24 (29)	Moderate	<.001[e]
Muscular pain	—	26 (30)	30 (30)	Trivial	.026[e]	31 (30)	Trivial	.004[e]
Hair loss	—	9 (20)	6 (18)	Trivial	.173	8 (19)	Trivial	.338
Taste change	—	5 (14)	4 (15)	Trivial	.611	6 (18)	Trivial	.283

Data are presented as number and mean (SD), unless otherwise indicated.

Effect sizes are provided in Supplemental Table 3.

ES, effect size (based on Cohen d); *EORTC*, European Organisation for Research and Treatment of Cancer; *QoL*, quality of life; *SD*, standard deviation.

[a] References are sex-specific and age-weighted means from an unselected Norwegian population;[15]; [b] Increasing means signify increased function; [c] Wilcoxon signed-rank analysis of difference in means between year 1 and baseline. Only patients with available year 1 data have been included; [d] Wilcoxon signed-rank analysis of difference in means between year 2 and baseline. Only patients with available year 2 data have been included; [e] *P* values of <.05 are statistically significant; [f] Increasing means signify increased symptoms.

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Baseline average scores for these estimates were close to or slightly below the general population reference values, whereas the higher year 1 values were slightly above the reference values. Moreover, sexual functioning and sexual activity increased after treatment and remained stable at year 2.

There was a small deterioration in physical functioning (−6 units at year 1 and −8 units at year 2) in the Chemo group compared with the baseline, whereas changes were trivial in the other 2 groups (Figure 2; Supplemental Table 4). Emotional function improved significantly more in the LNS group than in the Hyst group (*P*=.005 at year 1 and *P*=.017 at year 2).

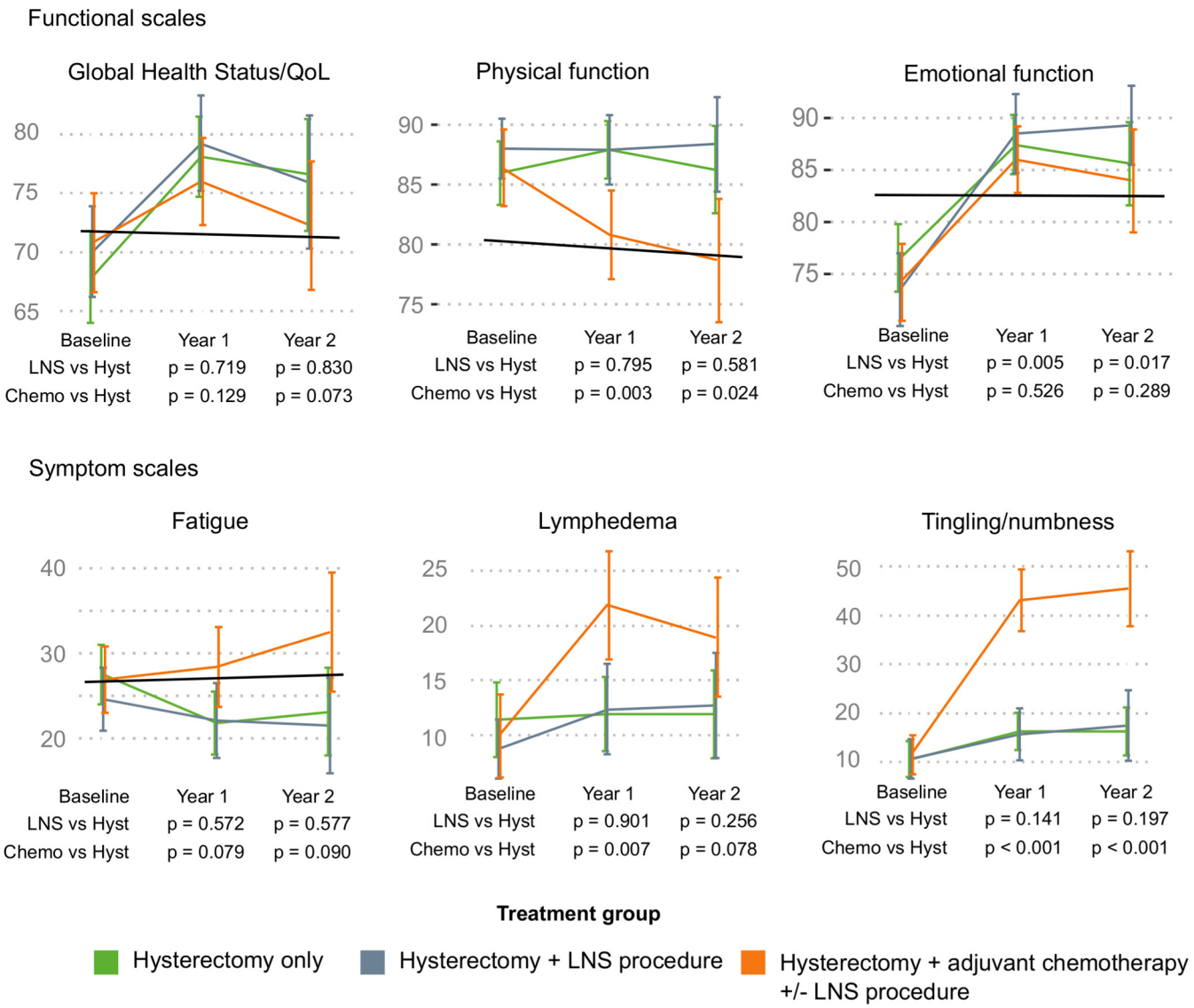
Patient-reported symptoms

Mean scores for lymphedema, tingling and numbness, and muscular pain increased significantly for the whole cohort from baseline to year 1 and remained elevated at year 2 (Table 2). The Chemo group had a large mean increase in tingling and numbness at years 1 and 2 (30−32 units), significantly larger than the increase in the Hyst group (5−6 units; *P*<.001; among groups at year 1 and 2) (Figure 2; Supplemental Table 4). In addition, significant between-group differences were found for lymphedema at year 1, with a moderate increase of 11 units in the Chemo group compared with 2 (trivial) in the Hyst group (*P*=.007). There was no between-group difference in the symptom scales between the Hyst and LNS groups.

Development of treatment-related symptoms

Overall, 76% of patients reported no moderate or severe lymphedema symptom at any time point (Figure 3, A). Preoperatively, 10% of patients reported moderate or severe

FIGURE 2
Patient-reported mean EORTC scale scores with 95% confidence intervals



Increases in functional scales signify an increase in function, and increases in symptom scales signify increase of symptoms. Reference values (*black lines*) are age- and sex-weighted means from a Norwegian general population survey (available for EORTC QLQ-C30, Fossa et al,[15] 2007). *P* values are derived from the Mann-Whitney test of change from baseline compared with the Hyst group. Values of all analyzed EORTC scales are provided in Supplemental Table 4.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; *Hyst group*, patients receiving hysterectomy alone; *QoL*, quality of life.

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lymphedema symptoms, whereas an additional 13% reported moderate or severe symptoms that debuted postoperatively. Of 27 patients reporting moderate or severe lymphedema symptoms at year 1, 12 had reported moderate or severe symptoms at baseline (Figure 3, B). The debut of moderate or severe lymphedema symptoms at year 1 was reduced or resolved in a third of patients at year 2. At year 2, 12 of 28 patients reporting lymphedema had previously reported no symptom or light symptoms.

At baseline, 7% of all patients reported moderate or severe tingling and numbness, whereas 19% of patients reported debut at year 1 and/or year 2 (Figure 3, C). At year 1, 27 of 30 patients reporting moderate or severe tingling and numbness symptoms had reported no symptom or light symptoms at baseline (Figure 3, D). Of these 27 patients, 16 reported persisting moderate or severe symptoms at year 2, with 14 being from the Chemo group.

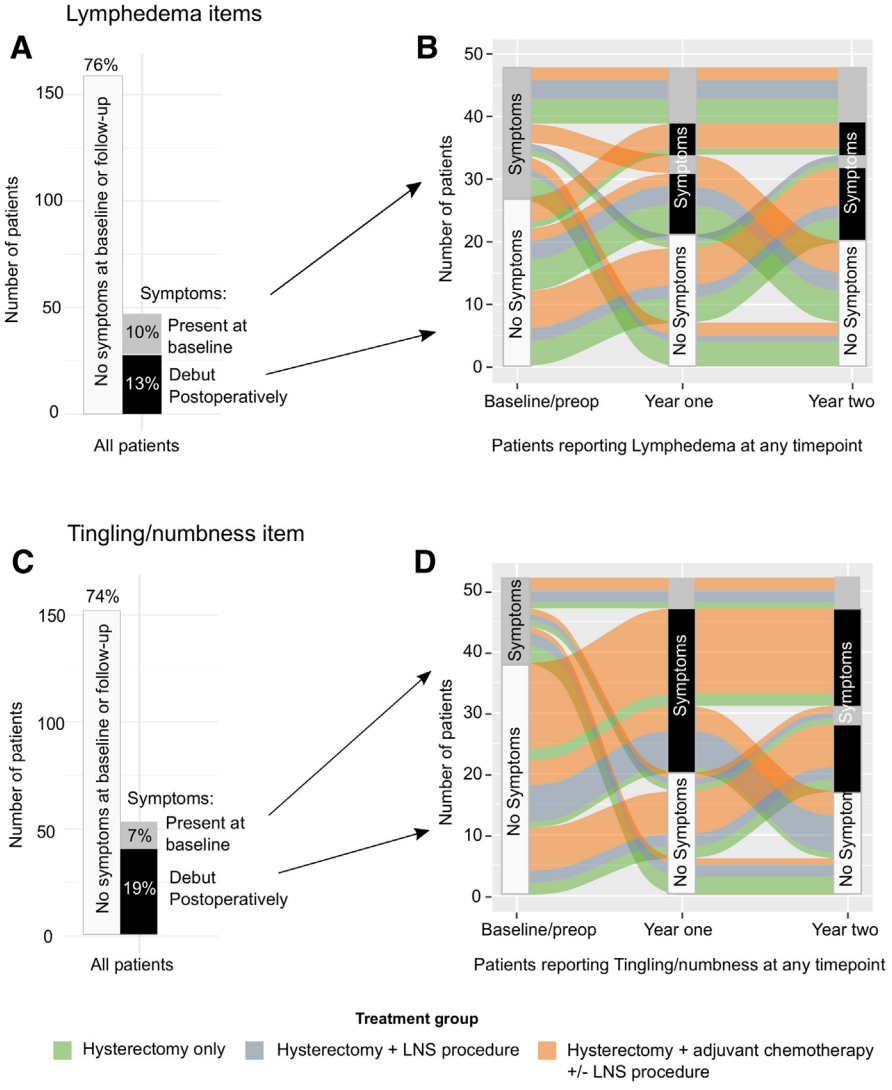
Treatment-specific effect on patient-reported outcomes

In linear mixed regression models (Figure 4; full data in Supplemental Table 5), adjuvant chemotherapy had an independent negative effect on physical function (regression coefficient, −7.5; 95% CI, −11.6 to −3.4; $P<.001$) and social function (−9.3; 95% CI, −14.7 to −3.8; $P=.002$) (Figure 4, A).

For symptom scales (Figure 4, B), adjuvant chemotherapy had a large increasing (detrimental) effect on tingling and numbness (regression coefficient, 27.1; 95% CI, 20.1−34.2; $P<.001$) and smaller increasing effects on fatigue (6.9; 95% CI, 0.9−12.9; $P=.025$), lymphedema (8.9; 95% CI, 3.6−14.2; $P=.001$), and taste change (5.0; 95% CI, 0.7−9.3; $P=.024$). No effect of LNS or surgical modality was identified in the models. There was no relevant time-treatment interaction between years 1 and 2 after treatment; thus, the effects of treatment were considered stable over this period (Supplemental Table 5).

As it may be argued that patients undergoing sentinel node biopsy have a risk of morbidity similar to patients without lymphadenectomy compared with those undergoing lymphadenectomy, this was explored in separate models. Grouping unstaged patients with those who had undergone sentinel node biopsy and comparing these with patients undergoing lymphadenectomy did not identify any significant effect on lymphedema score or alter estimates for adjuvant chemotherapy (Supplemental Table 6).

FIGURE 3
Case-wise analysis of treatment-related symptoms



A, Lymphedema symptoms defined as answering "quite a bit" or "very much" to either of the lymphedema associated items at any time point, in patients with complete 2-year follow-up (n=204). **B,** Case-wise evolution of lymphedema symptoms over time, by treatment received; only patients reporting symptoms are shown. **C,** Neuropathy symptoms defined as answering "quite a bit" or "very much" to the tingling and numbness item at any time point, in patients with complete 2-year follow-up (n=203). **D,** Case-wise evolution of tingling and numbness symptoms over time; only patients reporting symptoms are shown.

LNS, lymph node staging.

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Comment

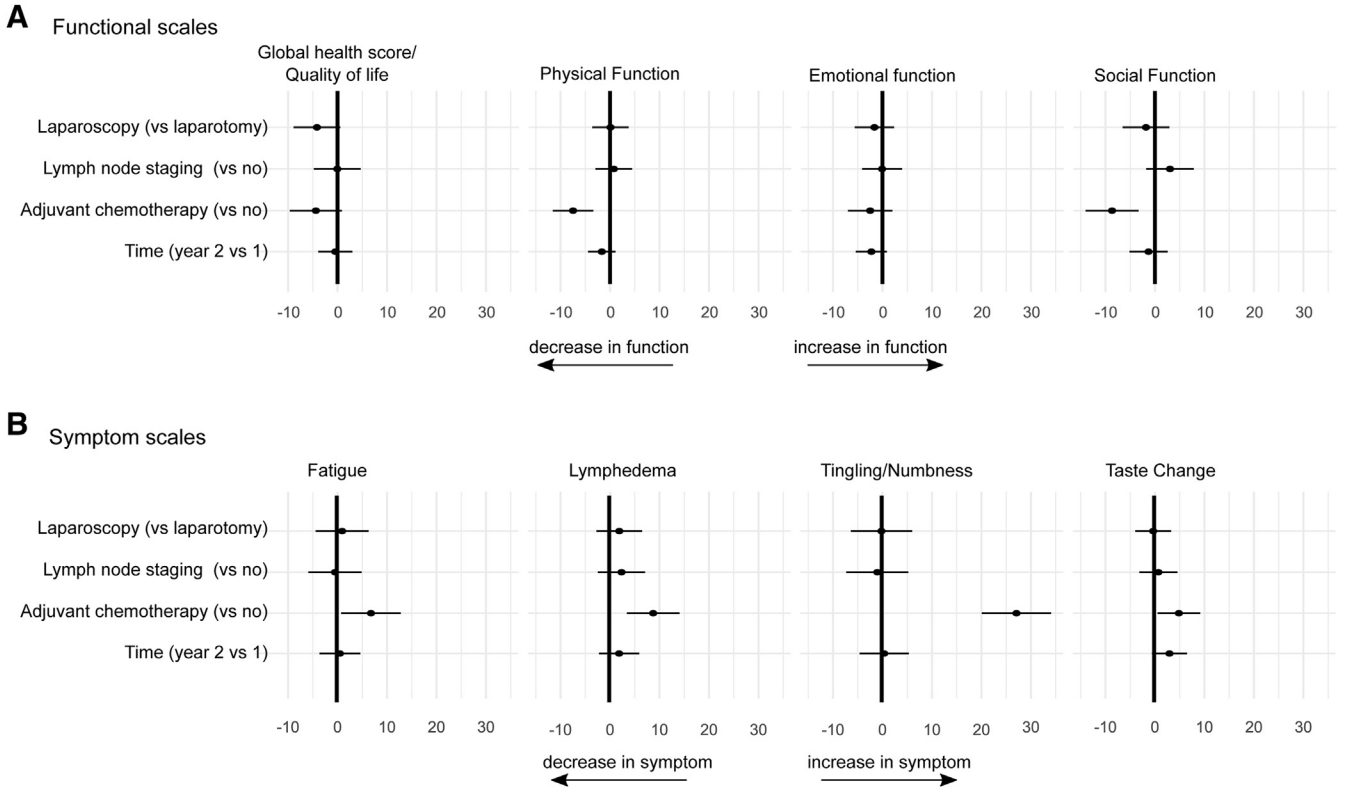
Principal findings

To the best of our knowledge, we presented the largest study prospectively investigating PROs in patients treated with no LNS for low-risk disease and adjuvant chemotherapy for high-risk disease, largely omitting adjuvant radiotherapy. Overall, patients with endometrial cancer had a good post-treatment QoL, functioned well, and expressed few symptoms, but increases in tingling and numbness and lymphedema were identified at the cohort level. We found that patients undergoing adjuvant chemotherapy more often reported long-term neuropathy, lymphedema, and fatigue and inferior physical function. In contrast, among patients not undergoing chemotherapy, we found no difference between those undergoing LNS and those treated by hysterectomy and BSO alone.

Results in the context of what is known

We demonstrated that patients with endometrial cancer overall have good self-reported QoL and functioning at 1

FIGURE 4
Effect estimates of time and treatment in linear mixed models



Effect estimates and 95% confidence interval for (**A**) EORTC functional and (**B**) EORTC symptom scales. Models are adjusted for baseline scores, all variables shown, and interactions between time and chemotherapy and time and lymph node staging. Effect estimates for all analyzed scales with *P* values obtained are provided in Supplemental Table 5.

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and 2 years after treatment. At baseline, global health status and QoL and emotional function were below the average population reference but increased with time in all treatment groups. These findings harmonized with previous prospective studies in populations with endometrial cancer.[21–23] The observed mean increase of QoL and functional scales could potentially be explained by low baseline scores because of a newly received cancer diagnosis with associated symptoms, anxiety, and affection of quality of life domains.

Our study did not demonstrate a clear link between lymphedema and LNS. An increased lymphedema score was reported for the Chemo group but not for the group treated with LNS without adjuvant chemotherapy. Although the proportion of sentinel node biopsy was higher in the LNS group, and the proportion of para-aortic lymphadenectomy was higher in the Chemo group, the total lymphadenectomy rates, excluding sentinel node biopsy, were similar for the 2 groups (73% vs 75%). Cross-sectional studies have reported significant mean increases in self-reported lymphedema scores in patients with lymphadenectomy compared with those without.[24,25] Importantly, other conditions than lymph tissue removal can result in lymphedema and likely have increasing impact at longer follow-up times, especially in a population with endometrial cancer with high age and comorbidity burden. These factors, combined with specified time points for follow-up, correction for baseline values, and avoidance of recall bias, could explain why results from longitudinal and cross-sectional studies may differ. Adjuvant chemotherapy is not an acknowledged risk factor for lymphedema in patients with endometrial cancer. Interestingly, in experimental models, paclitaxel inhibits neolymphangiogenesis, implying possible interference in the postoperative healing process.[26] In addition, adjuvant taxane-based chemotherapy has been implicated as a risk factor for arm lymphedema after breast cancer surgery with axillary node dissection, but clinical data are conflicting.[27,28]

The increase in self-reported neuropathy after receiving adjuvant chemotherapy harmonizes with longitudinal studies on patients with endometrial cancer receiving radiochemotherapy compared with either adjuvant modality alone.[22,29] Our results further confirmed this effect and provided novel data on the evolution of these symptoms over the

first 2 postoperative years, with late debut of symptoms in some patients and a substantial proportion of patients reporting unresolved symptoms at year 2.

Clinical implications

We have identified treatment-specific changes in self-reported outcomes that are useful when counseling patients on adjuvant treatment, as this is a group with a high comorbidity load and varying life expectancy. The main alternative approach for high-risk patients, adjuvant external beam radiotherapy, is not likely to cause neurologic symptoms but instead causes long-term bowel symptoms, with remaining problems at follow-up after 10 to 15 years[7–9]; thus the most promising approach to improving QoL in survivors of endometrial cancer is likely a further individualization of adjuvant treatment. Recently, we have reported that despite a substantial increase over time of adjuvant chemotherapy to early-stage or high-risk patients in a Norwegian tertiary hospital, survival and recurrence rates were unchanged for this group.[30] Further reduction of patients undergoing adjuvant chemotherapy may be achieved through better stratification, ideally by implementing new classifiers, such as imaging biomarkers or molecular subgroups (eg, TCGA or ProMisE) in treatment planning for these patients,[31,32] and developing and making available novel therapeutic agents to replace traditional chemotherapy where possible.

Research implications

Self-assessed lymphedema did not associate to LNS in our study. Whether this is attributable to measurement tool issues, prompt and effective treatment of lymphedema, patient adaptation, or cultural differences in reporting symptoms would be interesting to explore in future studies. Because of insufficient data, we were unable to explore the effect of sentinel lymph node biopsy subgroups on PROs, and data on this are still mainly lacking.[33] Finalizing inclusion and maturation of MoMaTEC2 data will provide better insight into the effect of different LNS techniques and long-term evolution of associated symptoms.

Strengths and limitations

Our study has several strengths. The importance of prospective registration for PROs should be stressed, as the baseline values are important determinants for long-term PROs. Previous studies have identified age, BMI, comorbidity, tumor stage, and marital and socioeconomic status to be important predictors of PROs in endometrial cancer,[21,23,34] and these variables can be approximated by including baseline PRO values. In addition, we limited our analyses to nonrelapsing survivors, thereby excluding bias introduced by successive treatments and changes in prognosis. PROs for patients with progressive and recurrent disease differed from the results of our study, and research questions and assessment approaches should be different for these groups.

The EORTC QLQ-EN24 questionnaire uses 2 items to assess lower extremity lymphedema and is not validated specifically for detecting secondary lymphedema. Recently, validated measurement tools for detecting lymphedema have been developed,[35,36] but these tools were not available when planning our study. Taken together with the heterogeneity of staging techniques and small groups undergoing each technique, no definite conclusion on LNS and lymphedema should be drawn. Despite this, we presented the lack of difference in self-assessed lymphedema among the treatment groups in this study as a contrast to the obvious differences in outcomes following adjuvant chemotherapy and as an interesting point that needs further examination.

Our results may be biased by the fact that treatment is not randomized but based on risk assessment, leading to unbalanced clustering of treatment modalities, such as more comprehensive lymphadenectomy performed in patients receiving chemotherapy. We have attempted to handle this through mixed model analysis, but few included patients receiving chemotherapy without LNS may to some degree influence the isolated PRO effects when comparing chemotherapy and lymph surgery.

In our study population, 71% of patients agreed to participate in the PRO follow-up. We found respondents and nonrespondents to have similar clinical characteristics but acknowledge that systematic differences between respondents and nonrespondents are a possible source of bias. An additional concern may be the differences in group sizes at the various time points. As this is caused by different follow-up times because of varying times since inclusion, we did not anticipate this to increase selection bias. For interpretation purposes, it is important to appreciate that conclusions for baseline and year 1 may be more robust than year 2 because of the larger groups.

Conclusions

We found that patients with endometrial cancer undergoing LNS without receiving chemotherapy are comparable with those not undergoing LNS and do not experience any significant deterioration from baseline to years 1 and 2, whereas patients receiving adjuvant chemotherapy have a higher risk of experiencing long-term neuropathy, lymphedema, and fatigue and inferior physical function. Considering these data, further striving to individualize adjuvant treatment is more pressing than adopting new surgical staging techniques. ■

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Author and article information

From the Centre for Cancer Biomarkers, Department of Clinical Science, University of Bergen, Bergen, Norway (Drs Forsse, Trovik, and Krakstad); Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway (Drs Forsse, Barbero, Werner, Woie, Trovik, and Krakstad); Department of Gynecology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (Dr Nordskar); Department of Obstetrics and Gynecology, Helse Stavanger-Stavanger University Hospital, Stavanger, Norway (Dr Berge Nilsen); Department of Obstetrics and Gynaecology, Akershus University Hospital, Lørenskog, Norway (Dr Ellstrøm Engh); Faculty Division Akershus University Hospital, University of Oslo (Dr Ellstrøm Engh); Department of Obstetrics and

Gynecology, Sørlandet Hospital, Kristiansand, Norway (Dr Vistad); Clinical Institute II, Department of Clinical Science, University of Bergen, Bergen, Norway (Dr Vistad); Department of Obstetrics and Gynecology, District General Hospital of Førde, Førde, Norway (Dr Rege); Department of Obstetrics and Gynecology, Helse Møre and Romsdal Hospital Trust, Ålesund, Norway (Dr Sævik-Lode); Department of Obstetrics and Gynecology, Nordland Hospital, Bodø, Norway (Dr Andreasen); Department of Radiology, Mohn Medical Imaging and Visualization Centre, Helse Bergen, Haukeland University Hospital, Bergen, Norway (Dr Haldorsen); Section for Radiology, Department of Clinical Medicine, University of Bergen, Bergen, Norway (Dr Haldorsen).

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Current address for H.M.J.W. is Department of Obstetrics and Gynecology, Maastricht University Medical Center, Maastricht, The Netherlands (Dr Werner); and GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands.

J.T. and C.K. share last authorship.

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Corresponding author: Camilla Krakstad, PhD. camilla.krakstad@uib.no

Appendix A

Treatment in MoMaTEC2 study

Standard treatment was hysterectomy with bilateral salpingo-oophorectomy (BSO). In algorithm-adhering centers, lymphadenectomy was omitted in patients with low-risk disease (endometrioid histology grade 1 or 2 in preoperative biopsy and grade 3 if <50% myometrial invasion on imaging) with immunohistochemical estrogen receptor (ER)- and progesterone receptor (PR)-positive expressions in the preoperative endometrial sample. In the case of ER or PR negativity in otherwise low-risk patients, a pelvic lymphadenectomy was performed. The level of immunohistochemical expression was revised in 2019 following an interim analysis comparing research-derived expression levels to routinely reported levels. The original cutoffs of <1% for ER and <10% for PR were changed to <30% for both, after consulting the MoMaTEC2 advisory board and participating centers.

Pelvic and para-aortic lymphadenectomies were routinely performed in high-risk patients: endometrioid grade 3 with deep myometrial infiltration, any nonendometrioid histology, or suspicion of stage >I of the International Federation of Gynecology and Obstetrics (FIGO) staging system (imaging, preoperative clinical status, and perioperative findings). Omentectomy was performed in patients with serous and clear cell histology. In control centers, sentinel node biopsy was performed for all risk groups, with hemipelvic lymphadenectomy in case of failed mapping. Mode of surgery (laparotomy, laparoscopy, or robot-assisted laparoscopy) varied within and among centers.

Adjuvant treatment

MoMaTEC2 does not require a certain adjuvant therapy policy to be followed. However, adjuvant treatment policy is observed in Norway and advocates the use of chemotherapy rather than radiotherapy. According to national guidelines, no adjuvant treatment is given to patients with endometrioid histology tumors and final FIGO I except IB with grade 3 differentiation. For patients deemed at high risk postoperatively (FIGO IB endometrioid grade 3, any nonendometrioid histology, or any FIGO stage >I), standard treatment is 6 rounds of carboplatin plus paclitaxel at 3-week intervals. The regimen could be shortened or altered because of patient status at the treating physician's discretion. For FIGO II with possible non–free resection margins, brachytherapy can be considered.

SUPPLEMENTAL TABLE 1

Clinical and pathologic characteristics of the studied cohort compared with patients declining participation in patient-reported outcome registration

Variable	Respondents	Nonrespondents
Included (n)	467	191
Age at treatment, median (IQR)	68 (14)	68 (16)
Body mass index, median (IQR)	28 (8)	28 (7)
	n (%)	n (%)
Mode of surgery (hysterectomy)		
Laparotomy	152 (35)	77 (48)
Laparoscopy	185 (42)	41 (26)
Robot-assisted laparoscopy	101 (23)	43 (27)
Lymph node staging		
Not performed	203 (44)	102 (53)
Sentinel node mapping	52 (11)	5 (3)
Pelvic lymphadenectomy	140 (30)	56 (29)
Para-aortic and pelvic	70 (15)	28 (15)
Lymph node metastasis		
Not investigated	203 (44)	102 (53)
Positive	37 (8)	16 (8)
Negative	226 (49)	73 (38)
FIGO stage		
I	381 (82)	134 (75)
II	27 (6)	12 (7)
III	45 (10)	22 (12)
IV	12 (3)	11 (6)
Histology		
EEC grade 1	197 (43)	72 (40)
EEC grade 2	130 (28)	50 (28)
EEC grade 3	46 (10)	20 (11)
Non-EEC	86 (19)	36 (20)
Adjuvant treatment		
None	313 (67)	113 (59)
External radiation	1 (0)	3 (2)
Brachytherapy	1 (0)	1 (1)
Chemotherapy	147 (32)	67 (35)
Hormonal treatment	3 (1)	3 (2)
Chemotherapy + radiation	1 (0)	2 (1)
Recurrence within 2 y		
Yes	25 (5)	16 (8)
No	429 (92)	151 (79)
Not completely resected at primary surgery	13 (3)	24 (13)

Data are presented as number (percentage) or median (IQR).

EEC, endometrioid endometrial cancer; *FIGO*, International Federation of Gynecology and Obstetrics; *IQR*, interquartile range.

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SUPPLEMENTAL TABLE 2

Number of responses per European Organization for Research and Treatment of Cancer scale at each assessment time point

Variable	Baseline n (%)	Year 1 n (%)	Year 2 n (%)
Eligible patients	448	367	237
Missing assessments	0 (0)	28 (8)	18 (8)
Respondents	448 (100)	339 (92)	219 (92)
EORTC scales			
Global health status or quality of life	443 (99)	338 (100)	219 (100)
Physical function	447 (100)	339 (100)	219 (100)
Emotional function	443 (99)	338 (100)	219 (100)
Cognitive function	444 (99)	338 (100)	219 (100)
Social function	444 (99)	338 (100)	219 (100)
Sexual interest	418 (93)	333 (98)	211 (96)
Sexual activity	421 (94)	333 (98)	211 (96)
Sexual enjoyment[a]	80 (18)	109 (32)	68 (31)
Fatigue	446 (100)	339 (100)	219 (100)
Lymphoedema	444 (99)	336 (99)	216 (99)
Urological symptoms	444 (99)	336 (99)	216 (99)
Gastrointestinal symptoms	443 (99)	336 (99)	216 (99)
Poor body image	436 (97)	334 (99)	216 (99)
Sexual and vaginal problems[a]	81 (18)	110 (32)	68 (31)
Pain in the back and pelvis	442 (99)	335 (99)	216 (99)
Tingling and numbness	443 (99)	335 (99)	216 (99)
Muscular pain	441 (98)	336 (99)	215 (98)
Hair loss	443 (99)	335 (99)	215 (98)
Taste change	443 (99)	336 (99)	215 (98)

Data are presented as number (percentage).

EORTC, European Organization for Research and Treatment of Cancer.

[a] Only answered if the respondent has been sexually active during the past 4 weeks.

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SUPPLEMENTAL TABLE 3

Cohen *d* effect sizes for included European Organization for Research and Treatment of Cancer scales calculated based on the study population baseline scores and compared with published anchor-based reference guidelines available for the European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire[19]

						Anchor-based reference					
			Study population baseline effect sizes			Improvement			Deterioration		
Functional scales[a]	Questionnaire	SD	0.2 (small)	0.5 (moderate)	0.8 (large)	Small	Medium	Large	Small	Medium	Large
Global health status or quality of life	C30	22.4	4	11	18	5	8	—	5	10	16
Physical function	C30	17.5	3	9	14	2	7	—	5	10	17
Emotional function	C30	21.4	4	11	17	6	9	—	3	12	—
Cognitive function	C30	18.7	4	9	15	3	7	—	1	7	—
Social function	C30	21.7	4	11	17	3	8	—	6	11	—
Sexual interest	EN24	21.9	4	11	17						
Sexual activity	EN24	19.1	4	10	15						
Sexual enjoyment	EN24	22.2	4	11	18						
Symptom scales[b]											
Fatigue	C30	22.8	5	11	18	4	9	—	5	10	15
Lymphoedema	EN24	18.3	4	9	15						
Urologic symptoms	EN24	19.0	4	10	15						
Gastrointestinal symptoms	EN24	15.8	3	8	13						
Poor body image	EN24	18.5	4	9	15						
Sexual and vaginal problems	EN24	20.8	4	10	17						
Pain in the back and pelvis	EN24	28.9	6	14	23						
Tingling and numbness	EN24	22.0	4	11	18						
Muscular pain	EN24	30.0	6	15	24						
Hair loss	EN24	20.1	4	10	16						
Taste change	EN24	14.4	3	7	12						

Data are presented as number.

C30, general cancer questionnaire—30 items; *EN24*, endometrial cancer questionnaire—24 items; *SD*, standard deviation of score at baseline assessment.

[a] Increasing means signify increased function; [b] Increasing means signify increased symptoms.

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SUPPLEMENTAL TABLE 4

Changes in European Organization for Research and Treatment of Cancer scale means at years 1 and 2 compared with baseline mean score by treatment subgroup

	Hyst group				LNS group						Chemo group					
Scale	Year 1	Effect size	Year 2	Effect size	Year 1	Effect size	*P* value	Year 2	Effect size	*P* value	Year 1	Effect size	*P* value	Year 2	Effect size	*P* value
Functional scales[a]																
Global health status or quality of life	10	S	9	S	10	S	.719	7	S	.830	6	S	.129	3	T	.073
Physical function	2	T	1	T	0	T	.795	0	T	.581	−6	S	.003[b]	−8	S	.024[b]
Emotional function	11	M	9	S	15	M	.005[b]	16	M	.017[b]	12	M	.526	10	S	.289
Cognitive function	3	T	2	T	2	T	.749	2	T	.907	0	T	.961	−4	S	.332
Social function	9	S	7	S	10	S	.868	8	S	.471	1	T	.131	−2	T	.106
Sexual interest	7	S	6	S	6	S	.751	9	S	.278	6	S	.919	5	S	.382
Sexual activity	6	S	5	S	7	S	.516	6	S	.977	6	S	.829	4	S	.234
Sexual enjoyment	−7	S	−13	M	−11	M	.559	−5	S	.056	−9	S	.832	−12	M	.553
Symptom scales[c]																
Fatigue	−6	S	−4	T	−2	T	.572	−3	T	.577	1	T	.079	6	S	.090
Lymphoedema	2	T	2	T	3	T	.901	4	S	.256	11	M	.007[b]	8	S	.078
Urologic symptoms	−2	T	−4	S	0	T	.865	−1	T	.752	0	T	.977	0	T	.629
Gastrointestinal symptoms	−2	T	−2	T	−1	T	.757	−2	T	.281	−3	S	.291	−2	T	.782
Poor body image	−4	S	−2	T	−2	T	.348	0	T	.549	1	T	.085	3	T	.098
Sexual and vaginal problems	4	S	15	M	2	T	.546	1	T	.670	4	S	.816	4	S	.460
Pain in the back and pelvis	−6	S	−7	S	−3	T	.921	−1	T	.712	−2	T	.316	0	T	.527
Tingling and numbness	5	S	6	S	5	S	.141	5	S	.197	30	L	<.001[b]	32	L	<.001[b]
Muscular pain	4	T	5	T	2	T	.835	6	S	.765	4	T	.589	2	T	.351
Hair loss	−3	T	−2	T	−4	S	.382	1	T	.826	0	T	.683	4	S	.602
Taste change	−2	T	2	T	−2	T	.662	0	T	.318	1	T	.496	6	S	.554

Magnitude of changes are assessed by effect size of the change (Cohen *d*). Statistical comparison of change from baseline between the treatment group and hysterectomy only group with Mann-Whitney test is performed. Further details are provided in Supplemental Table 3.

Chemo group, patients receiving hysterectomy with adjuvant chemotherapy, with or without *Hyst group*, patients receiving hysterectomy alone; *L*, large; *LNS*, lymph node staging; *LNS group*, patients receiving hysterectomy with LNS; *M*, moderate; *S*, small; *T*, trivial.

[a] Increasing means signify increased function; [b] *P* values of <.05 are statistically significant; [c] Increasing means signify increased symptoms.

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SUPPLEMENTAL TABLE 5

Effect estimates of time and treatment effects in linear mixed models for European Organization for Research and Treatment of Cancer scales

	Baseline			Adjuvant chemotherapy vs no chemotherapy			LNS vs no LNS			Laparoscopy vs laparotomy			Time (year 2 vs year 1)			Time-to-chemotherapy interaction ratio			Time-to-LNS interaction ratio		
Functional scale[a]	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value
Global health status or quality of life	0.4	(0.3 −0.5)	<.001[b]	−4.4	(−9.6 to 0.9)	.104	−0.1	(−4.8 to 4.7)	.982	−4.2	(−8.9 to 0.6)	.086	−0.5	(−3.9 to 3.0)	.798	−1.8	(−7.6 to 4.0)	.545	−2.9	(−8.2 to 2.3)	.279
Physical function	0.5	(0.4 −0.6)	<.001[b]	−7.5	(−11.6 to −3.4)	<.001[b]	0.8	(−2.9 to 4.5)	.684	0.1	(−3.6 to 3.8)	.961	−1.7	(−4.4 to 1.1)	.243	1.1	(−3.5 to 5.7)	.640	−0.3	(−4.5 to 4.0)	.906
Emotional function	0.3	(0.3 −0.4)	<.001[b]	−2.5	(−7.0 to 2.0)	.279	−0.1	(−4.1 to 4.0)	.970	−1.6	(−5.6 to 2.4)	.423	−2.2	(−5.4 to 0.9)	.165	−1.6	(−6.9 to 3.7)	.554	2.3	(−2.5 to 7.2)	.340
Cognitive function	0.5	(0.4 −0.6)	<.001[b]	−3.5	(−8.1 to 1.2)	.143	−1.6	(−5.7 to 2.6)	.458	−1.6	(−5.6 to 2.5)	.448	−1.7	(−5.1 to 1.7)	.329	−1.1	(−6.8 to 4.5)	.691	1.4	(−3.7 to 6.5)	.592
Social function	0.3	(0.2 −0.4)	<.001[b]	−8.7	(−14 to −3.3)	.002[b]	3.0	(−1.8 to 7.9)	.217	−1.8	(−6.5 to 2.9)	.453	−1.3	(−5.1 to 2.6)	.511	2.6	(−3.9 to 9.0)	.433	−2.7	(−8.6 to 3.2)	.367
Sexual interest	0.6	(0.5 −0.7)	<.001[b]	−1.1	(−7.6 to 5.4)	.739	1.2	(−4.8 to 7.1)	.699	−1.4	(−7.3 to 4.5)	.644	0.2	(−3.8 to 4.2)	.914	−2.7	(−9.2 to 3.9)	.428	0.5	(−5.5 to 6.5)	.876
Sexual activity	0.6	(0.5 −0.7)	<.001[b]	−0.8	(−7.0 to 5.3)	.787	2.5	(−3.0 to 8.0)	.376	1.2	(−4.5 to 6.8)	.688	0.1	(−3.4 to 3.6)	.961	0.2	(−5.5 to 6.0)	.939	−3.1	(−8.3 to 2.1)	.248
Sexual enjoyment	0.6	(0.5 −0.7)	<.001[b]	−1.1	(−7.6 to 5.4)	.739	1.2	(−4.8 to 7.1)	.699	−1.4	(−7.3 to 4.5)	.644	0.2	(−3.8 to 4.2)	.914	−2.7	(−9.2 to 3.9)	.428	0.5	(−5.5 to 6.5)	.876
Symptom scale[c]																					
Fatigue	0.4	(0.3 −0.5)	<.001[b]	6.9	(0.9 −12.9)	.025[b]	−0.3	(−5.7 to 5.0)	.899	1.1	(−4.3 to 6.4)	.690	0.6	(−3.5 to 4.8)	.760	1.0	(−5.9 to 7.9)	.776	−0.7	(−7 to 5.6)	.831
Lymphoedema	0.5	(0.4 −0.7)	<.001[b]	8.9	(3.6 −14.2)	.001[b]	2.5	(−2.3 to 7.3)	.308	2.0	(−2.6 to 6.7)	.388	2.0	(−2.1 to 6.1)	.336	−2.1	(−8.9 to 4.7)	.552	−3.9	(−10.1 to 2.2)	.213
Urologic symptoms	0.4	(0.4 −0.5)	<.001[b]	0.3	(−4.1 to 4.6)	.908	−0.6	(−4.4 to 3.3)	.775	0.2	(−3.7 to 4.0)	.932	−2.1	(−5 to 0.9)	.166	0.4	(−4.5 to 5.3)	0.874	2.1	(−2.4 to 6.5)	.361
Gastrointestinal symptoms	0.6	(0.5 −0.7)	<.001[b]	0.8	(−2.8 to 4.5)	.651	−0.4	(−3.6 to 2.9)	.820	2.5	(−0.7 to 5.7)	.127	0.1	(−2.5 to 2.7)	.929	1.3	(−3 to 5.6)	.561	0.8	(−3.1 to 4.7)	.694
Poor body image	0.3	(0.2 −0.4)	<.001[b]	3.4	(−1.3 to 8.1)	.153	0.7	(−3.5 to 4.9)	.736	2.0	(−2.3 to 6.3)	.365	1.7	(−0.7 to 4.2)	.169	0.3	(−3.8 to 4.5)	.876	−0.4	(−4.1 to 3.4)	.848
Sexual and vaginal problems	0.5	(0.4 −0.6)	.009[b]	4.8	(−1.1 to 10.7)	.108	−4.6	(−9.9 to 0.7)	.088	−0.2	(−5.4 to 5.0)	.943	1.0	(−3.2 to 5.1)	.652	−1.2	(−8.1 to 5.7)	.731	3.1	(−3.2 to 9.4)	.332

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(continued)

SUPPLEMENTAL TABLE 5

Effect estimates of time and treatment effects in linear mixed models for European Organization for Research and Treatment of Cancer scales *(continued)*

	Baseline			Adjuvant chemotherapy vs no chemotherapy			LNS vs no LNS			Laparoscopy vs laparotomy			Time (year 2 vs year 1)			Time-to-chemotherapy interaction ratio			Time-to-LNS interaction ratio		
Functional scale[a]	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value
Pain in the back and pelvis	0.4	(0.3 −0.5)	<.001[b]	2.1	(−5 to 9.2)	.565	1.2	(−5.2 to 7.7)	.706	−1.7	(−7.8 to 4.3)	.572	−0.2	(−6.1 to 5.6)	.943	−1.1	(−10.8 to 8.7)	.832	2.4	(−6.4 to 11.3)	.587
Tingling and numbness	0.4	(0.3 −0.5)	<.001[b]	27.2	(20.2 −34.2)	<.001[b]	−0.9	(−7.2 to 5.4)	.782	0.0	(−6.2 to 6.2)	.989	0.5	(−4.5 to 5.5)	.838	1.6	(−6.7 to 9.9)	.711	−1.4	(−8.9 to 6.2)	.722
Muscular pain	0.4	(0.3 −0.5)	<.001[b]	2.7	(−4.8 to 10.3)	.477	−1.9	(−8.7 to 4.9)	.579	1.2	(−5.1 to 7.6)	.705	0.2	(−6.1 to 6.5)	.960	−5.4	(−15.8 to 5.0)	.313	4.9	(−4.6 to 14.4)	.313
Hair loss	0.3	(0.2 −0.4)	<.001[b]	3.7	(−1.3 to 8.7)	.148	−3.3	(−7.7 to 1.2)	.148	1.5	(−2.8 to 5.8)	.484	0.1	(−3.9 to 4.0)	.975	−2.9	(−9.5 to 3.6)	.384	3.9	(−2 to 9.9)	.198
Taste change	0.1	(0.0 −0.2)	.151	5.0	(0.7 −9.3)	.024[b]	0.8	(−3.0 to 4.7)	.665	−0.2	(−3.8 to 3.4)	.916	3.1	(−0.5 to 6.6)	.089	0.8	(−5.1 to 6.7)	.796	−2.2	(−7.6 to 3.2)	.421

P values were obtained by Satterthwaite estimation of degrees of freedom.

CI, confidence interval; *LNS*, lymph node staging (including sentinel node biopsy).

[a] A positive effect estimate signifies increased function; [b] *P* values of <.05 are statistically significant; [c] A positive effect estimate signifies increased symptoms.

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SUPPLEMENTAL TABLE 6

Linear mixed model effect estimates of time and treatment effects for European Organization for Research and Treatment of Cancer scales, with alternate grouping of lymph node staging procedures

	Baseline			Adjuvant chemotherapy			LA vs SLN or no staging			Laparoscopy vs laparotomy			Time (year 2 vs year 1)			Time-to-chemotherapy interaction ratio			Time-to-LNS interaction ratio		
Functional scale[a]	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value
Global health status and quality of life	0.4	(0.3 −0.5)	<.001[b]	−4.5	(−9.7 to 0.6)	.083	−0.4	(−5.5 to 4.6)	.876	−4.8	(−10 to 0.4)	.069	−0.3	(−3.5 to 2.9)	.869	−1.2	(−6.9 to 4.4)	.673	−4.4	(−9.6 to 0.8)	.099
Physical function	0.5	(0.4 −0.6)	<.001[b]	−7.2	(−11.2 to −3.2)	<.001[b]	−0.7	(−4.7 to 3.3)	.737	−0.7	(−4.7 to 3.4)	.751	−1.4	(−4 to 1.2)	.284	1.6	(−3 to 6.1)	.494	−1.3	(−5.5 to 2.9)	.543
Emotional function	0.3	(0.3 −0.4)	<.001[b]	−2.1	(−6.5 to 2.2)	.337	−2.1	(−6.5 to 2.2)	.334	−2.7	(−7.0 to 1.7)	.231	−1.8	(−4.7 to 1.1)	.234	−1.0	(−6.2 to 4.2)	.698	1.4	(−3.4 to 6.2)	.574
Cognitive function	0.5	(0.4 −0.6)	<.001[b]	−3.4	(−7.9 to 1.1)	.136	−3.2	(−7.6 to 1.2)	.160	−2.7	(−7.1 to 1.7)	.226	−1.4	(−4.6 to 1.7)	.368	−0.9	(−6.4 to 4.7)	.754	1.0	(−4.1 to 6.1)	.707
Social function	0.3	(0.2 −0.4)	<.001[b]	−7.8	(−13.1 to −2.6)	.030[b]	−0.1	(−5.3 to 5.0)	.966	−3.0	(−8.1 to 2.2)	.266	−1.4	(−5 to 2.1)	.428	2.8	(−3.5 to 9.2)	.381	−3.3	(−9.1 to 2.5)	.267
Sexual interest	0.6	(0.5 −0.7)	<.001[b]	−0.6	(−7 to 5.7)	.846	−0.3	(−6.7 to 6.1)	.931	−1.8	(−8.3 to 4.7)	.595	0.1	(−3.6 to 3.8)	.950	−2.8	(−9.3 to 3.7)	.399	0.9	(−5.1 to 6.8)	.778
Sexual activity	0.6	(0.5 −0.7)	<.001[b]	−0.2	(−6.2 to 5.9)	.961	0.7	(−5.3 to 6.6)	.829	1.0	(−5.2 to 7.1)	.762	−0.8	(−4.1 to 2.4)	.614	−0.8	(−6.5 to 5.0)	.793	−1.0	(−6.3 to 4.3)	.708
Sexual enjoyment	0.6	(0.3 −0.9)	<.001[b]	0.1	(−15.9 to 16.1)	.992	−7.7	(−26.4 to 11.1)	.428	−19.9	(−39.2 to −0.5)	.050	2.8	(−2 to 7.5)	.267	−4.1	(−11.2 to 3.1)	.276	−3.7	(−11 to 3.6)	.334
Symptom scale[c]																					
Fatigue	0.4	(0.3 −0.5)	<.001[b]	7.1	(1.2 to 12.9)	.019[b]	−0.3	(−6.1 to 5.5)	.914	1.4	(−4.5 to 7.3)	.638	−0.2	(−4 to 3.6)	.915	−0.3	(−7.1 to 6.5)	.935	2.1	(−4.2 to 8.3)	.518
Lymphoedema	0.5	(0.4 −0.7)	<.001[b]	9.1	(3.9 −14.3)	<.001[b]	2.7	(−2.4 to 7.9)	.297	2.6	(−2.5 to 7.7)	.317	1.4	(−2.3 to 5.2)	.452	−2.5	(−9.2 to 4.3)	.472	−3.4	(−9.5 to 2.8)	.282
Urologic symptoms	0.4	(0.4 −0.5)	<.001[b]	0.1	(−4.1 to 4.3)	.951	−0.7	(−4.9 to 3.4)	.732	−0.2	(−4.4 to 4.0)	.933	−1.4	(−4.1 to 1.3)	.312	1.2	(−3.6 to 6.1)	.619	0.4	(−4 to 4.9)	.851
Gastrointestinal symptoms	0.6	(0.5 −0.7)	<.001[b]	0.6	(−3 to 4.1)	.748	1.1	(−2.4 to 4.6)	.542	3.3	(−0.3 to 6.8)	.072	0.1	(−2.2 to 2.5)	.910	1.2	(−3.1 to 5.5)	.579	1.0	(−2.9 to 4.9)	.612
Poor body image	0.3	(0.2 −0.4)	<.001[b]	2.3	(−2.2 to 6.9)	.320	5.8	(1.3 −10.3)	.012[b]	4.1	(−0.6 to 8.8)	.089	2.8	(0.6 −5.1)	.014[b]	2.1	(−1.9 to 6.1)	.312	−4.2	(−7.9 to −0.5)	.026[b]

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(continued)

SUPPLEMENTAL TABLE 6

Linear mixed model effect estimates of time and treatment effects for European Organization for Research and Treatment of Cancer scales, with alternate grouping of lymph node staging procedures *(continued)*

	Baseline			Adjuvant chemotherapy			LA vs SLN or no staging			Laparoscopy vs laparotomy			Time (year 2 vs year 1)			Time-to-chemotherapy interaction ratio			Time-to-LNS interaction ratio		
Functional scale[a]	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value	Effect estimate	95% CI	*P* value
Sexual and vaginal problems	0.4	(0.1 −0.7)	.012[b]	−6.0	(−20.7 to 8.7)	.427	8.2	(−8.8 to 25.1)	.350	−4.4	(−22 to 13.2)	.629	3.2	(−4.1 to 10.4)	.401	0.7	(−10.9 to 12.3)	.904	−3.2	(−15.4 to 9.0)	.612
Pain in back and pelvis	0.4	(0.3 −0.5)	<.001[b]	2.7	(−4.2 to 9.7)	.440	−0.5	(−7.3 to 6.4)	.894	−1.9	(−8.5 to 4.7)	.571	−0.4	(−5.7 to 5.0)	.897	−1.4	(−10.9 to 8.2)	.778	3.5	(−5.3 to 12.2)	.436
Tingling and numbness	0.4	(0.3 −0.5)	<.001[b]	27.3	(20.4 −34.1)	<.001[b]	−1.1	(−7.8 to 5.7)	.759	−0.1	(−6.9 to 6.7)	.971	−0.2	(−4.7 to 4.4)	.942	0.6	(−7.6 to 8.8)	.884	0.6	(−6.9 to 8.1)	.874
Muscular pain	0.4	(0.3 −0.5)	<.001[b]	2.5	(−4.9 to 9.8)	.508	−0.3	(−7.5 to 7.0)	.944	2.2	(−4.7 to 9.2)	.531	0.2	(−5.6 to 6.0)	.947	−5.9	(−16.2 to 4.3)	.258	6.5	(−2.9 to 15.9)	.180
Hair loss	0.3	(0.2 −0.4)	<.001[b]	2.7	(−2.1 to 7.6)	.272	−0.2	(−5 to 4.6)	.933	2.4	(−2.3 to 7.1)	.314	0.8	(−2.8 to 4.4)	.667	−2.4	(−8.9 to 4.1)	.472	2.9	(−3 to 8.9)	.332
Taste change	0.1	(0 −0.2)	.140	5.1	(0.9 −9.3)	.017[b]	1.3	(−2.8 to 5.4)	.525	0.5	(−3.5 to 4.5)	.801	2.2	(−1.1 to 5.4)	.192	−0.4	(−6.2 to 5.4)	.896	0.2	(−5.1 to 5.5)	.941

SLN was grouped with no lymph node staging and compared with lymphadenectomy (pelvic with or without para−aortic). *P* values were obtained by Satterthwaite estimation of degrees of freedom.

CI, confidence interval; *LA*, lymphadenectomy; *SLN*, sentinel lymph node biopsy.

[a] A positive effect estimate signifies increased function; [b] *P* values of <.05 are statistically significant; [c] A positive effect estimate signifies increased symptoms.

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