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

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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 (+11 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 measureable 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. 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. 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, sentinel node biopsy over lymphadenectomy, and potential long-term gastrointestinal symptoms for patients undergoing adjuvant radiotherapy. 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, and the possibility of reserving radiotherapy for...
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 manual16 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 cutoffs19 and found little deviation (Supplemental Table 3).

**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.
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. 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. 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.

**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...
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; \( P = .039 \)).

### 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          |

| 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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### 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 (\( P < .001 \)).
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 lymphedema. **TABLE 2**

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

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

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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).

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...
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. 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. 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. 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.

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. 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. 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. 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, 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. 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, 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, 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 responders 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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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 >1 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 >1), 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)         |

| 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 (100)      | 367 (82)     | 237 (83)     |
| 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.

| Functional scales                                      | Questionnaire | SD  | Study population baseline effect sizes | Anchor-based reference |
|--------------------------------------------------------|---------------|-----|----------------------------------------|------------------------|
|                                                        |               |     | 0.2 (small) | 0.5 (moderate) | 0.8 (large) | Improvement | Deterioration |
|                                                        |               |     |             |                 |             | 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                                          |               |     |             |                 |             |           |        |       |       |        |       |
| 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.

* Increasing means signify increased function; † 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

| Scale                                    | Hyst group | LNS group | Chemo group |
|------------------------------------------|------------|-----------|-------------|
|                                          | Year 1     | Year 2    | Year 1      | Year 2      | Year 1     | Year 2     | Year 1     | Year 2     |
|                                          | Effect size| Effect size| P-value     | Effect size| Effect size| P-value     | Effect size| Effect size| P-value     |
| 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<sup>b</sup> | -8 S         | .024<sup>b</sup> |
| Emotional function                       | 11 M       | 9 S       | 15 M        | .005<sup>b</sup> | 16 M       | .017<sup>b</sup> | 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                           |            |           |             |            |            |             |            |            |             |
| 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<sup>b</sup> | 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<sup>b</sup> | 32 L          | <.001<sup>b</sup> |
| 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’s 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.

<sup>a</sup> Increasing means signify increased function; <sup>b</sup> P values of <.05 are statistically significant; <sup>c</sup> 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

| Functional scale | Baseline Effect estimate | 95% CI | P value | Adjuvant chemotherapy vs no chemotherapy Effect estimate | 95% CI | P value | LNS vs no LNS Effect estimate | 95% CI | P value | Laparoscopy vs laparotomy Effect estimate | 95% CI | P value | Time (year 2 vs year 1) Effect estimate | 95% CI | P value | Time-to-chemotherapy interaction ratio Effect estimate | 95% CI | P value | Time-to-LNS interaction ratio Effect estimate | 95% CI | P value |
|------------------|--------------------------|-------|---------|----------------------------------------------------------|-------|---------|--------------------------------|-------|---------|----------------------------------------|-------|---------|----------------------------------------|-------|---------|----------------------------------------|-------|---------|----------------------------------------|-------|---------|
| Global health status or quality of life | 0.4 | (0.3 to 0.5) | .104 | (−4.8 to 4.7) | .982 | (−8.9 to 0.6) | .086 | (−3.9 to 3.0) | .798 | (−7.6 to 4.0) | .545 | (−8.2 to 2.3) | .279 |
| Physical function | 0.5 | (0.4 to −0.6) | <.001 | (−11.6 to 3.4) | <.001 | (−2.9 to 4.5) | .684 | (−3.6 to 3.8) | .961 | (−4.4 to 1.1) | .243 | (−3.5 to 5.7) | .640 | (−4.5 to 4.0) | .906 |
| Emotional function | 0.3 | (0.3 to −0.4) | <.001 | (−7.0 to 2.0) | 0.1 | (−4.1 to 4.0) | .970 | (−5.6 to 2.4) | .423 | (−5.4 to 1.6) | .165 | (−6.9 to 3.7) | .554 | (−2.5 to 7.2) | .340 |
| Cognitive function | 0.5 | (0.4 to −0.6) | <.001 | (−8.1 to 1.2) | .143 | (−5.7 to 2.6) | .458 | (−5.6 to 2.5) | .448 | (−5.1 to 1.7) | .329 | (−6.8 to 4.5) | .691 | (−3.7 to 6.5) | .592 |
| Social function | 0.3 | (0.2 to −0.4) | <.001 | (−14 to −3.3) | 0.002 | (−1.8 to 7.9) | .217 | (−6.5 to 2.9) | .453 | (−5.1 to 2.6) | .511 | (−3.9 to 9.0) | .433 | (−8.6 to 3.2) | .367 |
| Sexual interest | 0.6 | (0.5 to −0.7) | <.001 | (−7.6 to 5.4) | .739 | (−4.8 to 7.1) | .699 | (−7.3 to 4.5) | .644 | (−3.8 to 9.4) | .914 | (−9.2 to 3.9) | .428 | (−5.5 to 6.5) | .876 |
| Sexual activity | 0.6 | (0.5 to −0.7) | <.001 | (−7.0 to 5.3) | .787 | (−3.0 to 8.0) | .376 | (−4.5 to 6.8) | .688 | (−3.4 to 9.6) | .961 | (−5.5 to 6.0) | .939 | (−8.3 to 2.1) | .248 |
| Sexual enjoyment | 0.6 | (0.5 to −0.7) | <.001 | (−7.6 to 5.4) | .739 | (−4.8 to 7.1) | .699 | (−7.3 to 4.5) | .644 | (−3.8 to 9.4) | .914 | (−9.2 to 3.9) | .428 | (−5.5 to 6.5) | .876 |

**Symptom scale**

| Symptom | Effect estimate | 95% CI | P value | Effect estimate | 95% CI | P value | Effect estimate | 95% CI | P value |
|---------|----------------|-------|---------|----------------|-------|---------|----------------|-------|---------|
| Fatigue | 0.4 | (0.3 to −0.5) | <.001 | (−5.7 to 5.0) | .899 | 1.1 | (−4.3 to 6.4) | .690 | 0.6 |
| Lymphoedema | 0.5 | (0.4 to −0.7) | <.001 | (−3.6 to 7.3) | .308 | 2.0 | (−2.6 to 6.7) | .388 | 2.0 |
| Urologic symptoms | 0.4 | (0.3 to −0.5) | 0.001 | (−4.4 to 3.3) | .775 | 0.2 | (−3.7 to 4.0) | .932 | −2.1 |
| Gastrointestinal symptoms | 0.6 | (0.5 to −0.7) | <.001 | (−2.8 to 4.5) | .651 | −0.4 | (−3.6 to 2.9) | .820 | 2.5 |
| Poor body image | 0.3 | (0.2 to −0.4) | <.001 | (−1.3 to 8.1) | .153 | 0.7 | (−3.5 to 4.9) | .736 | 2.0 |
| Sexual and vaginal problems | 0.5 | (0.4 to −0.6) | 0.009 | (−1.1 to 10.7) | .108 | −4.6 | (−9.9 to 0.7) | .088 | −0.2 |

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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 (continued)

| Functional scale | Baseline | Adjuvant chemotherapy vs no chemotherapy | LNS vs no LNS | Laparoscopy vs laparotomy | Time (year 2 vs year 1) interaction ratio | Time-to-chemotherapy interaction ratio | Time-to-LNS interaction ratio |
|------------------|----------|------------------------------------------|--------------|---------------------------|------------------------------------------|--------------------------------------|-------------------------------|
|                  | 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 to 0.5) | <.001 | 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 to 0.5) | <.001 | 27.2 | (20.2 to 34.2) | <.001 | −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 to 0.5) | <.001 | 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 to 0.4) | <.001 | 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 14.4) | .198 |
| Taste change | 0.1 | (0.0 to −0.2) | .151 | 5.0 | (0.7 to −9.3) | .024 | 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 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

| Functional scale | Baseline | Adjuvant chemotherapy | Laparoscopy vs Time-to-chemotherapy | Time (year 2 vs year 1) | Time-to-chemotherapy interaction ratio | Time-to-LNS interaction ratio |
|------------------|----------|-----------------------|-------------------------------------|------------------------|----------------------------------------|-------------------------------|
|                  | 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 | <.001 | 0.83 (−0.4 to 1.1) | −0.1 (−1.0 to 0.8) | 0.19 (0.1 to 0.4) | 0.082 (−0.4 to 0.3) | −0.1 (−1.0 to 0.8) | 0.19 (0.1 to 0.4) |
| Physical function | 0.5 (0.4 − 0.6) | <.001 | <.001 | 0.73 (−0.7 to 1.7) | −1.4 (−3.1 to 0.3) | 1.6 (0.3 to 2.8) | 0.75 (−0.7 to 1.7) | −1.4 (−3.1 to 0.3) | 1.6 (0.3 to 2.8) |
| Emotional function | 0.3 (0.3 − 0.4) | <.001 | <.001 | 0.33 (−1.7 to 2.3) | 0.099 (0.0 to 0.2) | 0.12 (0.0 to 0.2) | 0.23 (−0.3 to 0.8) | 0.12 (0.0 to 0.2) | 0.12 (0.0 to 0.2) |
| Cognitive function | 0.5 (0.4 − 0.6) | <.001 | <.001 | 0.16 (−0.8 to 1.1) | 0.069 (0.0 to 0.1) | 0.03 (0.0 to 0.1) | 0.22 (−0.5 to 1.0) | 0.069 (0.0 to 0.1) | 0.03 (0.0 to 0.1) |
| Social function | 0.3 (0.2 − 0.4) | <.001 | <.001 | 0.06 (−0.2 to 0.3) | 0.06 (−0.2 to 0.3) | 0.06 (−0.2 to 0.3) | 0.06 (−0.2 to 0.3) | 0.06 (−0.2 to 0.3) | 0.06 (−0.2 to 0.3) |
| Sexual interest | 0.6 (0.5 − 0.7) | <.001 | <.001 | 0.84 (−0.3 to 1.9) | 0.93 (−0.3 to 1.1) | 0.93 (−0.3 to 1.1) | 0.84 (−0.3 to 1.9) | 0.93 (−0.3 to 1.1) | 0.93 (−0.3 to 1.1) |
| Sexual activity | 0.6 (0.5 − 0.7) | <.001 | <.001 | 0.96 (−0.3 to 1.7) | 0.76 (−0.3 to 1.7) | 0.76 (−0.3 to 1.7) | 0.96 (−0.3 to 1.7) | 0.76 (−0.3 to 1.7) | 0.76 (−0.3 to 1.7) |
| Sexual enjoyment | 0.6 (0.5 − 0.7) | <.001 | <.001 | 0.99 (−0.7 to 2.6) | 0.92 (−0.7 to 2.6) | 0.92 (−0.7 to 2.6) | 0.99 (−0.7 to 2.6) | 0.92 (−0.7 to 2.6) | 0.92 (−0.7 to 2.6) |
| Symptom scale | Fatigue | 0.4 (0.3 − 0.5) | <.001 | <.001 | 0.19 (0.1 to 0.4) | 0.91 (0.1 to 0.4) | 0.91 (0.1 to 0.4) | 0.19 (0.1 to 0.4) | 0.91 (0.1 to 0.4) |
| Lymphoedema | 0.5 (0.4 − 0.6) | <.001 | <.001 | 0.29 (−0.4 to 1.0) | 0.3 (−0.7 to 1.3) | 0.3 (−0.7 to 1.3) | 0.29 (−0.4 to 1.0) | 0.3 (−0.7 to 1.3) | 0.3 (−0.7 to 1.3) |
| Urologic symptoms | 0.4 (0.3 − 0.5) | <.001 | <.001 | 0.1 (−0.4 to 0.6) | 0.3 (−0.7 to 1.3) | 0.3 (−0.7 to 1.3) | 0.1 (−0.4 to 0.6) | 0.3 (−0.7 to 1.3) | 0.3 (−0.7 to 1.3) |
| Gastrointestinal symptoms | 0.6 (0.5 − 0.7) | <.001 | <.001 | 0.1 (−0.4 to 0.6) | 0.2 (−0.5 to 0.9) | 0.2 (−0.5 to 0.9) | 0.1 (−0.4 to 0.6) | 0.2 (−0.5 to 0.9) | 0.2 (−0.5 to 0.9) |
| Poor body image | 0.3 (0.2 − 0.4) | <.001 | <.001 | 0.32 (−0.2 to 0.8) | 0.9 (−0.3 to 2.1) | 0.9 (−0.3 to 2.1) | 0.32 (−0.2 to 0.8) | 0.9 (−0.3 to 2.1) | 0.9 (−0.3 to 2.1) |

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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 (continued)

| Functional scale<sup>a</sup> | Baseline | Adjuvant chemotherapy | Laparoscopy vs LA vs SLN or no staging laparotomy | Time (year 2 vs year 1) | Time-to-chemotherapy interaction ratio | Time-to-LNS interaction ratio |
|-----------------------------|----------|-----------------------|--------------------------------------------------|------------------------|---------------------------------------|-----------------------------|
|                             | 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<sup>b</sup> | 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) |
| Pain in back and pelvis     | 0.4 (0.3 - 0.5) | .<001<sup>b</sup> | 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) |
| Tingling and numbness       | 0.4 (0.3 - 0.5) | .<001<sup>b</sup> | 27.3 (20.4 - 34.1) | <001<sup>b</sup> | -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 8.7) |
| Muscular pain               | 0.4 (0.3 - 0.5) | .<001<sup>b</sup> | 2.5 (-4.9 to 9.8) | .508 | -0.3 (-7.5 to 7.0) | .944 | 2.2 (-4.7 to 4.2) | .531 | 0.2 (-5.6 to 6.0) | .947 | -5.9 (-16.2 to 4.3) | .258 | 6.5 (-2.9 to 15.9) |
| Hair loss                   | 0.3 (0.2 - 0.4) | .<001<sup>b</sup> | 2.7 (-2.1 to 7.6) | .272 | -0.2 (-5.0 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 (-3.0 to 8.9) |
| Taste change                | 0.1 (0 - 0.2)   | .140 | 5.1 (0.9 - 8.3) | .017<sup>a</sup> | 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) |

<sup>a</sup> A positive effect estimate signifies increased function; <sup>b</sup> P values of <.05 are statistically significant; <sup>c</sup> A positive effect estimate signifies increased symptoms.

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