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ORIGINAL ARTICLE

Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis

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Background: In early breast cancer (BC), there has been a trend to escalate endocrine therapy (ET) and to de-escalate chemotherapy (CT). However, the impact of ET versus CT on the quality of life (QoL) of early BC patients is unknown. Here, we characterize the independent contribution of ET and CT on patient-reported outcomes (PROs) at 2 years after diagnosis.

Patients and methods: We prospectively collected PROs in 4262 eligible patients using the European Organization for Research and Treatment of Cancer QLQ-C30/BR23 questionnaires inside CANTO trial (NCT01993498). The primary outcome was the C30 summary score (C30-SumSc) at 2 years after diagnosis.

Results: From eligible patients, 37.2% were premenopausal and 62.8% postmenopausal; 81.9% received ET and 52.8% CT. In the overall cohort, QoL worsened by 2 years after diagnosis in multiple functions and symptoms; exceptions included emotional function and future perspective, which improved over time. ET ($P_{int} = 0.004$), but not CT ($P_{int} = 0.924$), had a persistent negative impact on the C30-SumSc. In addition, ET negatively impacted role and social function, pain, insomnia, systemic therapy side-effects, breast symptoms and further limited emotional function and future perspective recovery. Although CT had no impact on the C30-SumSc at 2-years it was associated with deteriorated physical and cognitive function, dyspnea, financial difficulties, body image and breast symptoms. We found a differential effect of treatment by menopausal status; in premenopausal patients, CT, despite only a non-significant trend for deteriorated C30-SumSc ($P_{int} = 0.100$), was more frequently associated with QoL domains deterioration than ET, whereas in postmenopausal patients, ET was more frequently associated with QoL deterioration, namely using the C30-SumSc ($P_{int} = 0.004$).

Conclusion(s): QoL deterioration persisted at 2 years after diagnosis with different trajectories by treatment received. ET, but not CT, had a major detrimental impact on C30-SumSc, especially in postmenopausal women. These findings highlight the need to properly select patients for adjuvant ET escalation.

Key words: early breast cancer, quality of life, endocrine therapy, chemotherapy, patient-reported outcome

Introduction

Due to improvements in early detection and treatment achieved over the last decades, 80%–90% of women diagnosed with early-stage breast cancer (BC) in developed countries can expect long-term disease-free survival. With the growing number of women with history of BC, it is becoming increasingly important to address the potential long-term and late effects of treatments that survivors will face [1].

There have been remarkable changes in the pattern of treatment of early BC in the last few years. Notable is the recent trend to escalate ET in patients with hormone receptor (HR)-positive early BC by extending the duration of treatment and/or by treatment intensification with the addition of ovarian function suppression (OFS) for premenopausal patients [2]. Concurrently, there has been a trend to de-escalate chemotherapy (CT), driven by a desire to avoid short- and long-term toxicities and the results of prospective trials that identified genomically low-risk patients who could be spared CT and treated with endocrine therapy (ET) alone [3].

Despite their proven efficacy in improving BC outcomes, both ET and CT have the potential to negatively impact survivors' quality of life (QoL) [4–6]. ET strategies such as tamoxifen, aromatase inhibitors (AI) and OFS have well described and persistent side-effects that may facilitate deterioration of QoL, although most clinical trials data indicate that the impact of ET on QoL of BC patients is only modest [7]. The deterioration in QoL might further negatively impact adherence and persistence to ET leading to early treatment discontinuation [8, 9]. CT also worsens QoL, and this effect is well demonstrated through active treatment and in the immediate post-CT phase. However, there are few data on the long-term independent effect of CT on QoL. In addition, the differential impact of ET versus CT on QoL has not been fully characterized, especially among cohorts treated with modern adjuvant regimens using validated and modern tools to measure patient-reported outcomes (PROs) [10]. Such information could provide objective guidance for patients and physicians to weight the impact of each of these treatments on QoL and to define future research priorities in this evolving field.

We therefore compared the impact of different classes of treatment (CT and ET) on European Organization for Research and Treatment of Cancer (EORTC)-defined QoL instruments using CANTO (NCT01993498), a multicenter, nationwide, prospective cohort study of 12,012 women with stage I–III BC, of which 5801 women available for research, that aims to quantify the toxicities of cancer treatment of up to 5 years after the end of primary treatment [11]. We hypothesized that exposure to different classes of treatment, namely ET and/or CT, would have different impact on QoL 2 years after diagnosis. Moreover, we hypothesized that such impact would differ by menopausal status, given the different class of ET agents used (mostly tamoxifen in premenopausal and AIs in postmenopausal women) and the different *sequelae* of CT (with possible early loss of ovarian function in premenopausal women) by menopausal status.

Patients and methods

Study design and patient selection

This was a prospective, longitudinal cohort study. We used data collected at diagnosis, end of primary treatment, which include completion of BC surgery, chemotherapy, or radiation therapy, whatever ended last [median time from diagnosis = 10.4 months, interquartile range (IQR), 8.0–12.3] and at 2 years after diagnosis (median time from diagnosis = 22.6 months, IQR 20.1–24.8; patients receiving ET were at a median of 16.3 months, IQR 14.9–17.9, into ET).

We included 4262 patients with stage I–III BC enrolled in CANTO cohort from March 2012 to January 2015, corresponding to the first data lock of CANTO. Supplementary Figure S1, available at *Annals of Oncology* online details exclusion and inclusion criteria. All patients provided written informed consent.

To assess the potential bias introduced by the exclusion of patients with missing evaluation 2 years after diagnosis, the characteristics of such patients were compared with those of participating patients. Patients missing evaluation tended to be older, smokers, less educated, living alone, have lower income, present higher TNM (tumor–node–metastasis) [12] or triple-negative BC, have undergone mastectomy and be more frequently depressed (supplementary Table S1, available at *Annals of Oncology* online).

Variables assessment

PROs assessments. PROs were assessed using the EORTC QoL Core 30 (EORTC QLQ-C30, version 4.0) and its BC-specific module (QLQ-BR23) [13]. Higher scores reflect a better level of QoL and function for global health and functional scales, respectively, and greater severity for symptoms. The primary end point of the study was the QLQ-C30 summary score (C30-SumSc) and specific domains were secondary end points [13]. Anxiety and depression were assessed using Hospital Anxiety and Depression Scale.

Assessments of other variables: Information on age, Charlson's comorbidity index, body mass index, smoking, marital status, education level, income, disease staging, center volume, type of surgery, axillary management, receipt of ET, CT, trastuzumab and radiotherapy was collected at diagnosis by medical record review.

Statistical analysis

First, we described QoL over time and by treatment, examining the C30-SumSc and dichotomizing QoL scores by clinical severity. Severe impairment was defined as function impairment or symptom intensity meeting a predefined clinically meaningful level. Clinically meaningful levels were defined using as reference the mean score of the validation cohort of EORTC QLQ-C30/B23, specific to patients with stage I–II BC, plus a detrimental variation to the level of the lower boundary of medium clinically meaningful differences according to evidence-based guidelines for C30 domains [14], or 10 points for B23 domains (a variation previously considered of clinical value) [15]. Functional scores below such thresholds defined 'poor function', while symptom scores above threshold values defined 'severe symptoms'.

Then, repeated measurements of QoL scores collected from diagnosis to the 2-year postdiagnosis visit were analyzed as continuous outcomes using multivariate generalized estimating equations (GEE) with independent correlation structure. Model-derived least square mean values for QoL scores and respective mean least square (MLS) differences between diagnosis and the 2-year postdiagnosis visit by ET and/or CT (used

as independent variables) were obtained. To test the hypothesis that the population-averaged domain scores differ over time by treatment with ET/CT, *P* values for the interaction of ET/CT by time were computed (P_{int}). Models included as covariates all variables previously described ('other variables' plus anxiety and depression), all of which were collected at diagnosis.

An exploratory analysis was also conducted to determine the effect of treatment on QoL across four treatment groups: CT-only, ET-only, CT plus ET and no CT/ET. Similarly, MLS changes from diagnosis were estimated from GEE.

All tests were two-sided with a 95% confidence interval (CI) and a *P*-value of <0.05 was considered significant. All analyses were conducted using Stata 15.1 (StataCorp, College Station, TX).

Results

Patient characteristics

Of the 4262 women available for the analysis, 1587 (37.2%) were premenopausal and 2675 (62.8%) postmenopausal. Patient characteristics are shown in Table 1 and supplementary Table S2, available at *Annals of Oncology* online.

PRO assessments

PROs over time. The overall QoL was negatively impacted 2 years after diagnosis in the general population (C30-SumSc, $P < 0.001$). In addition, we observed a significant negative impact on role, cognitive and social functions, and also pain, dyspnea, fatigue, body image, systemic therapy side-effects, constipation and breast and arm symptoms (all $P < 0.001$) (Figure 1, supplementary Figure S2 and Table S3, available at *Annals of Oncology* online). Considering all domains, no substantial recovery was noticed from the end of primary treatment to the 2 years after diagnosis time point, except for emotional function, future perspective and appetite loss, which slightly improved during this period (all $P < 0.001$).

ET and/or CT impact on general QoL. Only ET was associated with deteriorated C30-SumSc 2-years after diagnosis ($P_{int} = 0.004$) that persisted over time (Figure 1, Table 2 and supplementary Table S4, available at *Annals of Oncology* online). In contrast, after a transient deterioration, there was no detrimental effect of CT on C30-SumSc at 2 years ($P_{int} = 0.924$). Young age, comorbidities, smoking, low income, and anxiety/depression were also associated with QoL deterioration at 2 years (supplementary Table S4, available at *Annals of Oncology* online shows multivariate models for C30-SumSc, remaining models not shown).

We then assessed the impact of treatment on general QoL (C30-SumSc) according to menopausal status. In premenopausal patients, neither ET ($P_{int} = 0.242$) nor CT ($P_{int} = 0.100$) were associated with a significant decrease of C30-SumSc after multivariate adjusting. In postmenopausal women, ET ($P_{int} = 0.004$), but not CT ($P_{int} = 0.394$), was associated with a substantial decrease in general QoL (MLS change at 2 years of −4.07 versus −1.39 for ET versus no ET). Prevalence of poor functions and severe symptoms and mean changes in QoL scores 2 years after diagnosis for patients treated or not with CT and/or ET are shown for the overall cohort and according to menopausal status in Table 2, Figure 2 and supplementary Figures S2 and S3, available at *Annals of Oncology* online.

QLQ-C30. Patient-reported functional scales: In the overall cohort, at 2 years, statistically significant worse QoL was observed among patients treated with ET (versus no ET) for role functioning (*P* for interaction between treatment group-time [P_{int}] = 0.005) and social functioning ($P_{int} = 0.032$); CT (versus no CT) impacted negatively physical functioning ($P_{int} < 0.001$) and cognitive functioning ($P_{int} < 0.001$) (Table 2, Figure 2A).

In premenopausal patients, a statistically significant worse QoL was observed with CT (versus no CT) for physical functioning ($P_{int} < 0.001$) and cognitive functioning ($P_{int} < 0.001$). ET did not impact any functional domain (Table 2, Figure 2B).

In postmenopausal patients, statistically significant worse QoL was seen with ET for global health status ($P_{int} = 0.006$), role functioning ($P_{int} = 0.001$) and social functioning ($P_{int} = 0.012$). CT did not impact any functional domain (Table 2, Figure 2C).

Patient-reported symptom scales: In the overall cohort, at 2 years, statistically significant worse QoL was observed with ET (versus no ET) for pain ($P_{int} = 0.001$). Insomnia improved among those not treated with ET (versus ET) ($P_{int} = 0.014$); CT (versus no CT) impacted negatively dyspnea ($P_{int} < 0.001$) and financial difficulties ($P_{int} = 0.015$). Appetite loss improved among those treated with CT (versus no CT) ($P_{int} < 0.001$) (Table 2, Figure 2A).

In premenopausal patients, statistically significant worse QoL was observed with CT (versus no CT) for dyspnea ($P_{int} = 0.030$), and financial difficulties ($P_{int} = 0.045$). Appetite loss improved among those treated with CT (versus no CT) ($P_{int} < 0.001$). ET did not impact any symptom domain (Table 2, Figure 2B).

In postmenopausal patients, statistically significant worse QoL was seen with ET for nausea ($P_{int} = 0.001$) and pain ($P_{int} = 0.001$) and CT (versus no CT) impacted negatively dyspnea ($P_{int} = 0.011$). Appetite loss improved among those treated with CT (versus no CT) ($P_{int} = 0.009$) (Table 2, Figure 2C).

QLQ-BR23. Patient-reported functional scales: In the overall cohort and by menopausal status, statistically significant worse QoL was observed with CT (versus no CT) for body image ($P_{int} < 0.001$) at 2 years. ET did not impact any functional domain (Table 2, supplementary Table S3A–C, available at *Annals of Oncology* online).

Patient-reported symptom scales: In the overall cohort, at 2 years, statistically significant worse QoL was observed with ET (versus no ET) for systemic therapy side-effects ($P_{int} < 0.001$) and breast symptoms ($P_{int} = 0.024$); CT (versus no CT) impacted negatively breast symptoms ($P_{int} < 0.001$) (Table 2, supplementary Figure S3a, available at *Annals of Oncology* online).

In premenopausal and postmenopausal patients, statistically significant worse QoL was observed with CT (versus no CT) for breast symptoms ($P_{int} < 0.001$ and 0.040, respectively) and ET impacted negatively systemic therapy side-effects ($P_{int} = 0.030$ and 0.004, respectively) (Table 2, supplementary Figure S3B–C, available at *Annals of Oncology* online).

Comparative analysis of sequential CT/ET, CT and ET-only and no systemic treatment groups were consistent with the above

Table 1. Demographic, clinical and pathological characteristics at baseline and treatment details according to receipt of chemotherapy (CT)/endocrine therapy (ET)

	Overall cohort					
	All		CT		ET	
Number (%)	4262 (100)		2252 (52.8)		3490 (81.9)	
Age, median (IQR)	56 (48–65)		52 (44.5–61)		56 (48–65)	
Age, n (%)						
≤35	124	2.9	118	5.2	83	2.4
>35 to ≤40	221	5.2	193	8.6	166	4.8
>40 to ≤50	1077	25.3	700	31.1	915	26.2
>50 to ≤60	1211	28.4	645	28.6	979	28.1
>60 to ≤70	1212	28.4	477	21.2	1003	28.7
>70	417	9.8	119	5.3	344	9.9
Charlson's score, n (%)						
0	3127	80.1	1678	81.5	2559	80.0
≥1	779	19.9	382	18.5	638	20.0
Missing	356	8.4	192	8.5	293	8.4
BMI, n (%)						
Underweight	96	2.3	53	2.4	83	2.4
Normal	2124	50.0	1146	51.0	1736	49.9
Overweight	1225	28.8	617	27.5	978	28.1
Obese	804	18.9	429	19.1	682	19.6
Missing	13	0.3	7	0.3	11	0.3
Smoking status, n (%)						
No/previous smoker	3511	84.0	1834	82.8	2874	83.8
Smoker	670	16.0	382	17.2	556	16.2
Missing	81	1.9	36	1.6	60	1.7
Education, n (%)						
Primary school	587	14.6	258	12.2	498	15.1
High school	1903	47.2	955	45.1	1550	46.9
College or higher	1539	38.2	905	42.7	1257	38.0
Missing	233	5.5	134	6.0	185	5.3
Income, n (%)						
<1500	529	13.5	274	13.2	441	13.7
≥1500 to <3000	1665	42.5	849	40.8	1374	42.8
≥3000	1726	44.0	957	46.0	1397	43.5
Missing	342	8.0	172	7.6	278	8.0
Marital status, n (%)						
Living alone	850	21.0	410	19.2	708	21.4
Living as couple	3200	79.0	1730	80.8	2608	78.6
Missing	212	5.0	112	5.0	174	5.0
Histology, n (%)						
Invasive carc., NST	3310	77.7	1825	81.1	2645	75.8
Invasive lobular carc.	566	13.3	227	10.1	541	15.5
Mixed NST/lobular	129	3.0	69	3.1	117	3.4
Others	254	6.0	128	5.7	186	5.3
Missing	3	0.1	3	0.1	1	0.0
TNM stage, n (%)						
I	2192	51.5	640	28.4	1788	51.3
II	1675	39.3	1235	54.9	1361	39.0
III	393	9.2	376	16.7	339	9.7
Missing	2	0.0	1	0.0	2	0.1
Histologic grade, n (%)						
1	776	18.4	94	4.2	646	18.6
2	2254	53.3	1055	47.1	2078	59.7
3	1197	28.3	1093	48.8	758	21.8
Missing	35	0.8	3	0.1	8	0.2
IHC-defined subtype of breast cancer, n (%)						
HR+/HER2-	3317	77.8	1397	62.0	410	11.7
HR+/HER2+	435	10.2	373	16.6	3075	88.1
HR-/HER2+	173	4.1	170	7.5	4	0.1
HR-/HER2-	337	7.9	312	13.9	1	0.0
Surgery type, n (%)						
BCS	3145	73.8	1428	63.4	2575	73.8
Mastectomy	1117	26.2	824	36.6	915	26.2
Axillary management, n (%)						
Axillary dissection	1674	39.3	1328	59.0	1373	39.4
Sentinel node/none	2587	60.7	923	41.0	2116	60.6
Radiotherapy, n (%)						
Yes	3881	91.1	2086	92.6	3182	91.2
No	381	8.9	166	7.4	308	8.8
(Neo)adjuvant CT type, n (%)[a]						
Anthracyclines-taxanes	1931	45.3	1931	86.0	1455	41.8
Anthracyclines-based	96	2.3	96	4.3	80	2.3
Taxanes-based	218	5.1	218	9.7	171	51.0
Other	1	0.0	1	0.0	1	0.0
Missing regimen	6	0.1	6	0.3	5	0.1
No	2010	47.2	0	0.0	1778	4.9
HER2-directed therapy, n (%)						
Yes	477	11.2	475	21.1	300	8.6
No	3785	88.8	1777	78.9	3190	91.4
Adjuvant endocrine therapy type, n (%)						
Tamoxifen ± LHRH	1334	31.2	797	35.4	1334	38.3
AI ± LHRH	1997	50.0	831	37.0	1997	57.3
LHRH	10	0.2	7	0.3	10	0.3
Tamoxifen → AI ± LHRH	144	3.3	74	3.3	144	4.2
Missing agent	5	0.1	3	0.1	5	0.1
No	772	18.1	540	24.0	0	0.0
HADS-defined anxiety, n (%)						
Normal	1613	39.4	792	36.6	1326	39.6
Borderline	1067	26.1	580	26.8	881	26.3
Anxiety	1412	34.5	793	36.6	1144	34.1
Missing	170	4.0	87	3.9	139	4.0
HADS-defined depression, n (%)						
Normal	3378	82.6	1765	81.5	2763	82.5
Borderline	442	10.8	242	11.2	362	10.8
Depression	272	6.6	158	7.3	226	6.7
Missing	170	4.0	87	3.9	139	4.0

[a]Among all patients receiving chemotherapy, the most frequent regimen administered was FEC (fluorouracil plus epirubicin plus cyclophosphamide) followed by a taxane (docetaxel/paclitaxel) in 81.4% of patients while the second most frequent regimen was TC (docetaxel plus cyclophosphamide), administered to 6.5% of patients. Among all patients receiving chemotherapy, the distribution by menopausal status of FEC-T and TC was of 86.3%/3.5% and 76.8%/9.2%, for premenopausal women and postmenopausal women, respectively.

BCS, breast conserving surgery; BMI, body mass index; CT, chemotherapy; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; n, number. missing values do not add to the percentage count of non-missing categories.

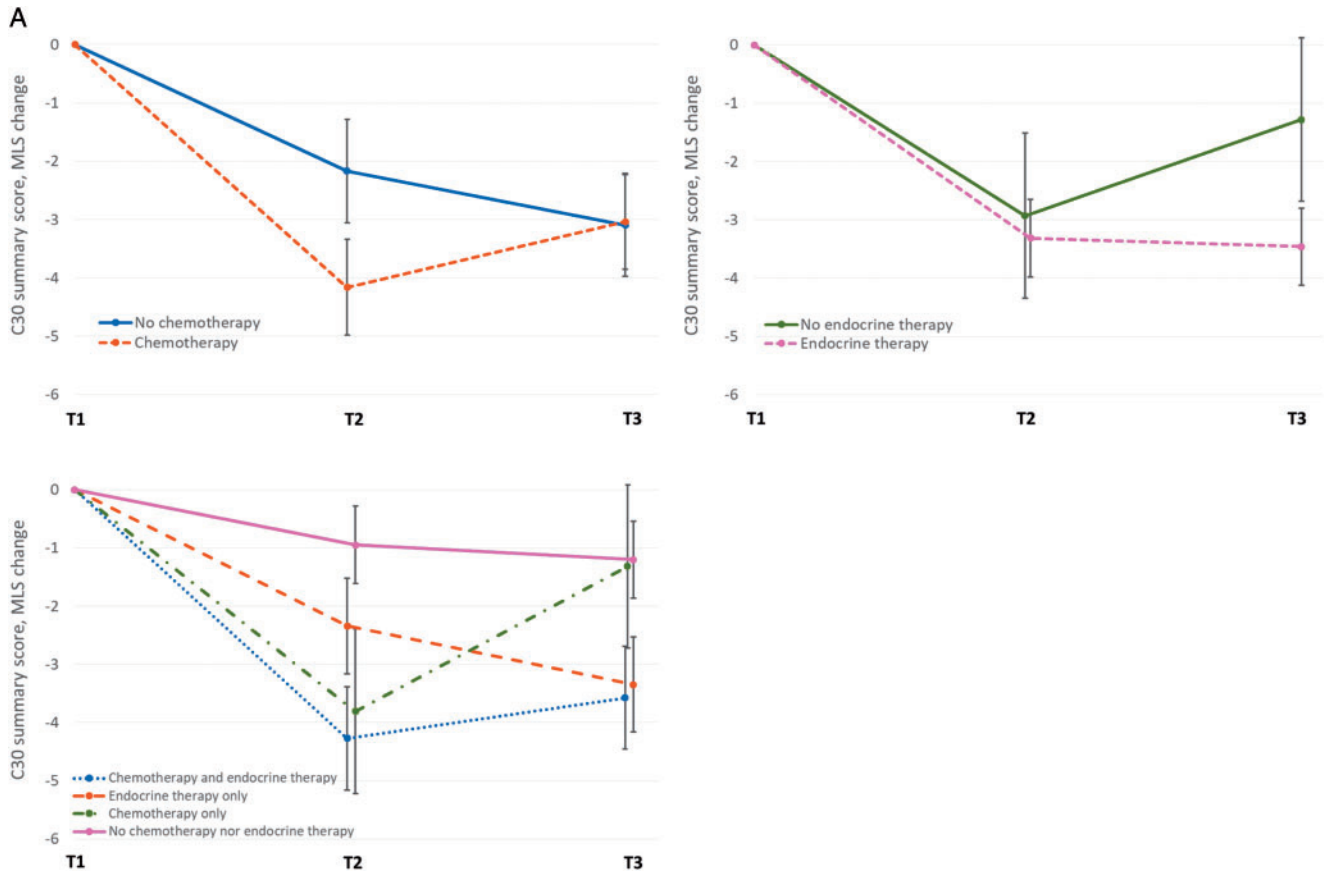

Figure 1. Mean least square change of European Organization for Research and Treatment of Cancer QLQ C30 summary score from diagnosis (T1) to 'end of primary treatment' (T2) and the '2 years after diagnosis visit' (T3) in patients treated and not treated with chemotherapy or endocrine therapy in the overall cohort (non-mutually exclusive groups) (A), and in premenopausal (B) and postmenopausal (C) patients. Error bars refer to the 95% confidence interval of the estimate. Estimates and confidence intervals derived from multivariate generalized estimating equations models.

findings (supplementary Figures S4 and S5, available at *Annals of Oncology* online). Independent of menopausal status, the sequential therapy with CT and ET have the highest impact on several QoL domains; however, global health status was mainly impacted by ET for the overall cohort and for postmenopausal women and by CT for premenopausal. Emotional function and future perspective recover was smaller among the groups treated with ET.

Discussion

In this study, we investigated the variation in QoL from early BC diagnosis, thus before any intervention, to 2 years afterward among 4262 patients enrolled in the prospective CANTO cohort, a large, real-world contemporary study of patients treated for BC across France. Using validated general and BC-specific PROs, we found that patients report overall significantly deteriorated QoL 2 years after BC diagnosis that is impacted by both ET and CT independently. ET represented a considerable and persistent burden for some BC survivors' QoL, affecting the C30-SumSc and a substantial number of domains, while CT effect seems to have a more transient negative impact on QoL. Nevertheless, differential patterns of change in QoL were observed according to adjuvant treatment class and after stratification by menopausal status at diagnosis.

Corresponding with the improved BC survival, the need for patients and healthcare providers to understand the differential effect that distinct classes of adjuvant treatments may have on late QoL is emerging as a priority. Previous research suggested that most physical and psychosocial symptoms that commonly follow adjuvant BC treatment usually resolve in the first year after BC diagnosis and that most of BC survivors recover high functional levels of QoL [16–18]. Nevertheless, it has been also reported that some patients may experience more persistent and distressing troubles that include longer-term physical, cognitive, and sexual disturbances [5, 6, 19, 20]. In this study, we found that a substantial number of BC survivors report poor QoL (and deteriorated from diagnosis) 2 years after diagnosis, including a decrease in the C30-SumSc, but also 27.8% of patients reporting poor global health status, 38.4% severe cognitive dysfunction, 51% severe pain, 45.5% severe dyspnea and 33.6% severe fatigue.

Interestingly, when compared with diagnosis and thus before any intervention, our data seem to indicate that the receipt of distinct classes of adjuvant treatment was associated with differential patterns of QoL 2-years after. Prior studies have yielded inconsistent results in this regard. Some suggested that CT leads to

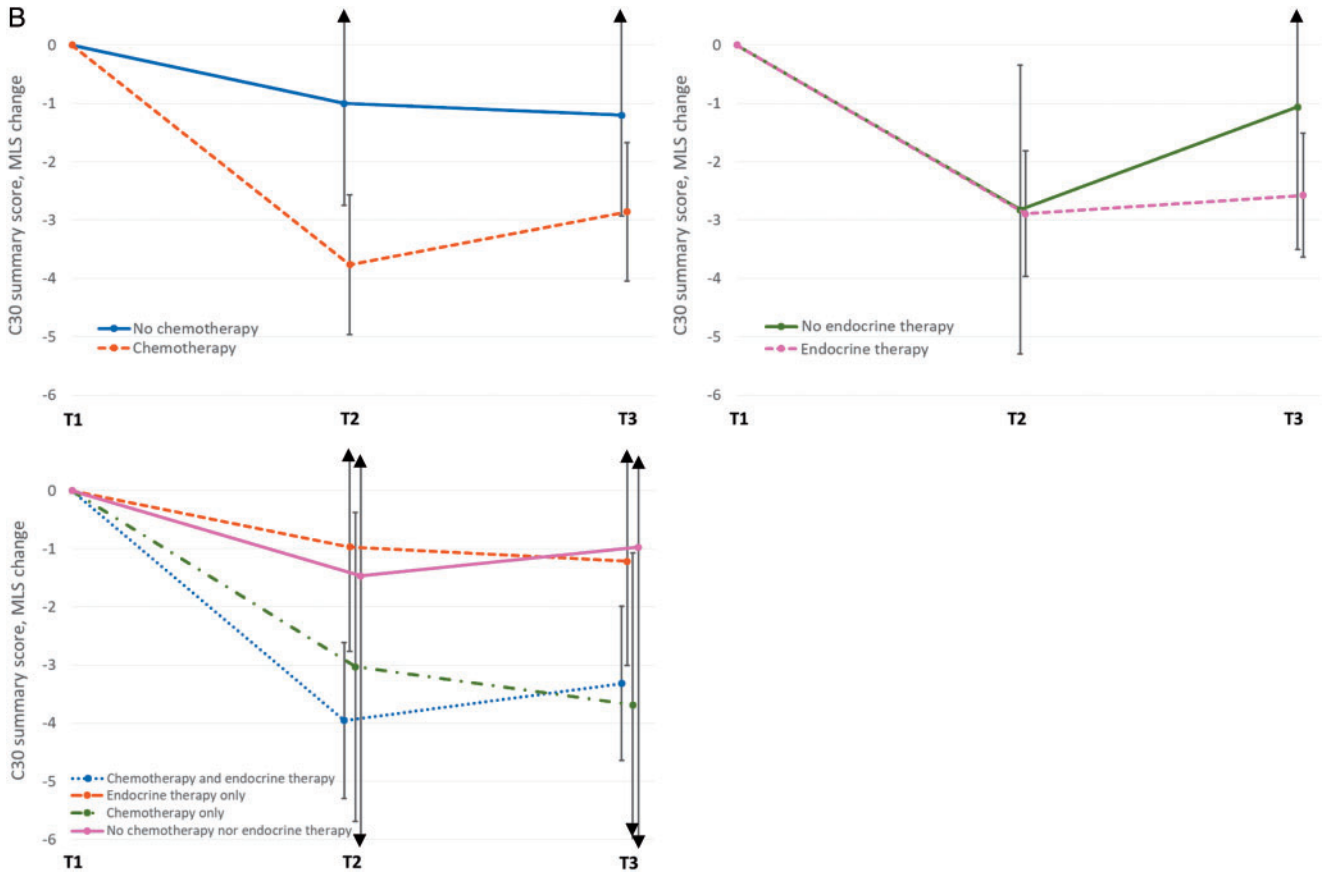

Figure 1. Continued.

cumulative, yet transient, QoL deterioration, which resolves shortly after treatment completion, whereas ET has a more prolonged negative effect on QoL, and other studies have suggested no major differences in QoL by treatment group [5, 6, 19–21]. For example, a pooled analysis of International BC Study Group trials showed a measurable impact of CT on QoL during active treatment, which was, however, transitory [19]. Nevertheless, persistence of QoL deterioration was associated with treatment strategy over time, with patients treated with chemoendocrine treatment scoring lower than patients treated only with tamoxifen. A previous cross-sectional study evaluating the QoL of BC survivors on average 3 years after BC diagnosis suggested no overall major differences in QoL between adjuvant treatments groups [6]. This is consistent, with a recent analysis of the TAILORx trial that compared the impact of ET versus ET + CT in the cognitive function, fatigue and endocrine symptoms [21]. Overall, although the addition of CT to ET led to greater cognitive impairment, fatigue and endocrine symptoms in the first 3–6 months, this change diluted between groups at a follow-up up to 36 months. Our study, making a comprehensive evaluation of with the use of a QoL summary score and several Qol domains, expands this knowledge. Patients were assessed at 2 years after diagnosis and both CT and ET seemed to impact QoL, particularly the C30-SumSc, each however playing a distinct role in different domains. ET had a persistently negative and clinically meaningful impact in C30-SumSc and in multiple functions and symptoms, including role and social function and pain, insomnia and systemic therapy side-effects. In contrast, ET seems to attenuate the recovery in domains that typically improve overtime such as emotional function and future perspectives. In contrast, the impact of CT seemed to be transient and restricted to physical and cognitive function, financial difficulties, body image and breast symptoms, with no impact in the C30-SumSc at 2 years post diagnosis. Our approach to evaluate the contributions of ET and CT after stratification by menopausal status adds further to the literature. In premenopausal patients, receipt of CT although fading overtime overall, it was associated with significant deterioration of several QoL domains. In addition, while CT seems to be the only driver of cognitive impairment in premenopausal women, both ET and CT contribute additively to cognitive deterioration in postmenopausal women. In postmenopausal patients, deterioration of QoL was associated substantially with ET. Treatment and treatment implications can greatly differ by menopausal status partially explaining these differences. Eighty-nine percent of premenopausal women in our cohort who received ET were treated with tamoxifen compared with 88% of postmenopausal women who received AIs; therefore, it is possible that the use of AI might have driven our findings on the postmenopausal cohort. This is in line with recent longitudinal cohort data of 186 BC patients that suggested significantly reduced physical QoL for patients treated with AIs 1 year after initiation of ET compared with tamoxifen, but it contrasts with clinical trial data

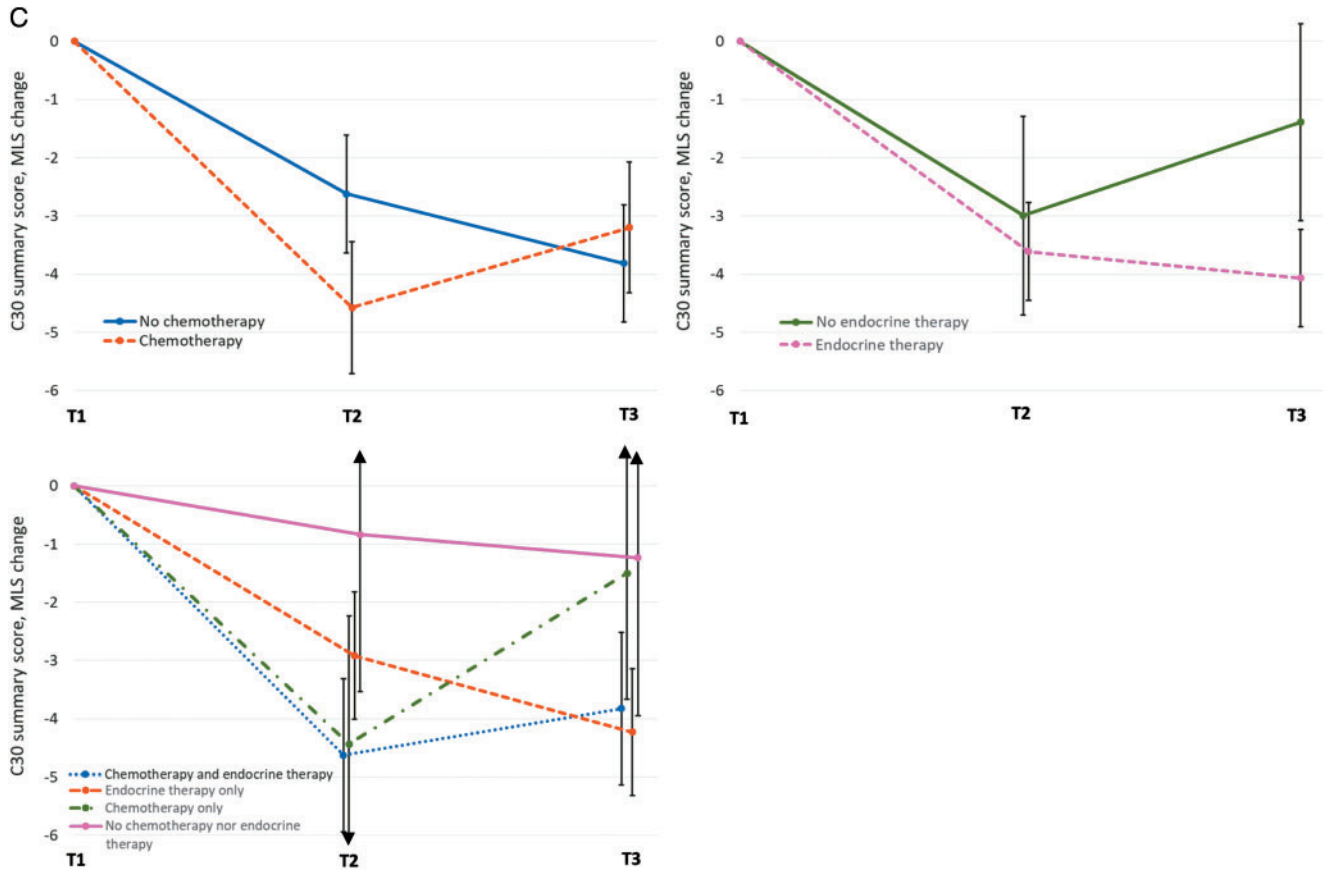

Figure 1. Continued.

that have traditionally suggested only small differences in QoL by type of ET. If this is correct, the recent trend toward escalation of ET, either by extending the total duration of treatment or, in premenopausal women by intensifying treatment with the use of OFS with tamoxifen or AIs, might therefore substantially add to the burden of ET on QoL. In premenopausal women, the impact of CT in QoL might indeed reflect transient or permanent ovarian function failure, suggesting that uptake of OFS in these patients may have a major impact on their QoL.

For this study, we used a large national French cohort that is representative of the overall BC population (77.8% HR+/HER2− BC, 51.5% stage I, 86.0% of CT-treated patients received anthracyclines–taxanes) and that offered a unique opportunity to have a detailed and up-to-date perspective of the impact of CT and ET in QoL of BC patients. Nevertheless, we acknowledge some limitations. The proportion of patients with missing QoL questionnaire at 2 years after diagnosis was over 25%. While not optimal, this can be expected given the real-world research. Specific populations, as older and less educated/lower-income patients might be underrepresented in this study thus deserving a focused approach in future research. Also, this study included patients who were diagnosed between 2012 and 2015, and treatment patterns have evolved since. The proportion of patients currently on adjuvant OFS plus AI or tamoxifen is higher than what was noted in the present study, which might underestimate the toxicity of ET in premenopausal women. Likewise, the most frequent adjuvant anthracycline–taxane combination regimen in CANTO was FEC-T (5-fluorouracil-epirubicin-cyclophosphamide followed by a taxane), while in current practice EC/AC-T (epirubicin/doxorubicin-cyclophosphamide followed by a taxane) is predominant. A minority of patients was treated with anthracyclines-sparing regimens which is, in some practices, an emerging regimen to treat early BC. In addition, we did not explore the QoL impact by endocrine or CT regimen, since it is out of the scope of this article. Moreover, there is not just one QoL metric, but many outcomes that have to be assessed to capture the overall impact of treatment on QoL, nevertheless we integrated a QoL summary score as primary outcome. Furthermore, we used EORTC QLQ BR23 module instead of the BR45 which was unavailable at CANTO study inception and is now in phase IV testing. Given that the QLQ BR45 might better capture specific BC treatment toxicities (e.g. joint pain and muscle ache), our results may be a conservative picture of the ET impact. In addition, due to the observational design and although we performed a comprehensive adjustment of our models, we cannot exclude unmeasured confounding, including factors such as treatment adherence. Lastly, no formal adjustment for multiplicity has been performed given the observational nature of the study.

In conclusion, QoL was deteriorated at 2 years after BC diagnosis in multiple functions and symptoms. QoL deterioration was associated with ET in postmenopausal women, and receipt of CT seemed to have a larger impact in premenopausal women. This

Table 2. Mean least square change of specific domain according to exposure to chemotherapy and/or to endocrine therapy

Symptom, dimension or scale	Treatment	Overall cohort			Premenopausal			Postmenopausal		
		MLS change	95% CI	*P*-value	MLS change	95% CI	*P*-value	MLS change	95% CI	*P*-value
EORTC QLQ-C30, summary score										
Summary score	No chemotherapy	−3.094	−3.937 to −2.252	0.924	−1.184	−2.840 to 0.473	0.100	−3.825	−4.787 to −2.863	0.394
	Chemotherapy	−3.038	−3.817 to −2.260		−2.863	−3.995 to −1.731		−3.199	−4.272 to −2.127	
	No endocr. therapy	−1.294	−2.634 to 0.045	0.004	−1.05	−3.385 to 1.285	0.242	−1.417	−3.032 to 0.198	0.004
	Endocrine therapy	−3.458	−4.090 to −2.826		−2.572	−3.593 to −1.552		−4.066	−4.864 to −3.268	
EORTC QLQ-C30, functional scales										
Global health status	No chemotherapy	−3.379	−4.558 to −2.199	0.054	−1.838	−4.123 to 0.447	0.697	−3.95	−5.320 to −2.580	0.118
	Chemotherapy	−1.799	−2.895 to −0.703		−1.288	−2.851 to 0.274		−2.309	−3.842 to −0.776	
	No endocr. therapy	−1.215	−3.094 to 0.665	0.129	−2.971	−6.193 to 0.250	0.317	−0.31	−2.612 to 1.993	0.006
	Endocrine therapy	−2.825	−3.713 to −1.937		−1.176	−2.583 to 0.232		−3.934	−5.073 to −2.795	
Physical functioning	No chemotherapy	−5.006	−5.926 to −4.087	<0.001	−3.707	−5.252 to −2.161	<0.001	−5.493	−6.632 to −4.353	0.055
	Chemotherapy	−7.403	−8.260 to −6.547		−7.655	−8.719 to −6.591		−7.164	−8.439 to −5.889	
	No endocr. therapy	−5.402	−6.870 to −3.933	0.190	−6.754	−8.946 to −4.562	0.720	−4.696	−6.613 to −2.779	0.079
	Endocrine therapy	−6.488	−7.182 to −5.795		−6.316	−7.275 to −5.356		−6.611	−7.559 to −5.663	
Role functioning	No chemotherapy	−4.76	−6.241 to −3.279	0.393	−0.271	−3.146 to 2.603	0.104	−6.43	−8.141 to −4.719	0.158
	Chemotherapy	−3.878	−5.256 to −2.499		−3.164	−5.139 to −1.189		−4.578	−6.493 to −2.664	
	No endocr. therapy	−1.21	−3.570 to 1.150	0.005	−1.107	−5.164 to 2.951	0.551	−1.266	−4.141 to 1.610	0.001
	Endocrine therapy	−4.975	−6.090 to −3.859		−2.453	−4.231 to −0.675		−6.669	−8.091 to −5.247	
Emotional functioning	No chemotherapy	3.816	2.373 to 5.259	0.004	4.947	2.043 to 7.851	0.124	3.408	1.774 to 5.041	0.061
	Chemotherapy	6.727	5.381 to 8.072		7.711	5.716 to 9.707		5.757	3.926 to 7.588	
	No endocr. therapy	6.592	4.283 to 8.901	0.253	7.525	3.411 to 11.639	0.716	6.11	3.355 to 8.866	0.188
	Endocrine therapy	5.102	4.014 to 6.191		6.691	4.896 to 8.487		4.044	2.685 to 5.404	
Cognitive functioning	No chemotherapy	−2.759	−4.256 to −1.262	<0.001	−1.378	−4.453 to 1.697	0.001	−3.258	−4.918 to −1.599	0.121
	Chemotherapy	−6.503	−7.897 to −5.108		−7.789	−9.903 to −5.676		−5.232	−7.090 to −3.373	
	No endocr. therapy	−4.235	−6.631 to −1.840	0.633	−6.421	−10.785 to −2.058	0.736	−3.079	−5.877 to −0.282	0.410
	Endocrine therapy	−4.88	−6.009 to −3.751		−5.601	−7.506 to −3.697		−4.39	−5.771 to −3.010	
Social functioning	No chemotherapy	−4.959	−6.269 to −3.649	0.666	−4.35	−6.965 to −1.734	0.368	−5.183	−6.672 to −3.693	0.811
	Chemotherapy	−5.353	−6.575 to −4.131		−5.809	−7.609 to −4.009		−4.91	−6.582 to −3.238	
	No endocr. therapy	−3.088	−5.189 to −0.987	0.032	−4.888	−8.603 to −1.172	0.795	−2.165	−4.685 to 0.355	0.012
	Endocrine therapy	−5.629	−6.616 to −4.642		−5.426	−7.043 to −3.808		−5.761	−6.999 to −4.523	
EORTC QLQ-C30, symptoms scales										
Fatigue	No chemotherapy	6.418	4.852 to 7.985	0.591	4.104	0.932 to 7.275	0.262	7.278	5.515 to 9.041	0.763
	Chemotherapy	7.005	5.546 to 8.464		6.308	4.128 to 8.489		7.684	5.711 to 9.658	
	No endocr. therapy	5.913	3.411 to 8.414	0.477	5.063	0.579 to 9.546	0.797	6.352	3.381 to 9.323	0.416
	Endocrine therapy	6.915	5.735 to 8.095		5.704	3.742 to 7.665		7.728	6.262 to 9.194	

Continued

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Table 2. *Continued*

Symptom, dimension or scale	Treatment	Overall cohort			Premenopausal			Postmenopausal		
		MLS change	95% CI	*P*-value	MLS change	95% CI	*P*-value	MLS change	95% CI	*P*-value
Nausea	No chemotherapy	1.43	0.593 to 2.266	0.128	−0.665	−2.448 to 1.119	0.358	2.208	1.308 to 3.109	0.032
	Chemotherapy	0.542	−0.236 to 1.321		0.351	−0.876 to 1.578		0.73	−0.278 to 1.738	
	No endocr. therapy	−0.044	−1.379 to 1.291	0.105	1.206	−1.316 to 3.727	0.316	−0.695	−2.210 to 0.820	0.001
	Endocrine therapy	1.177	0.547 to 1.808		−0.201	−1.305 to 0.902		2.101	1.352 to 2.849	
Pain	No chemotherapy	12.842	11.224 to 14.460	0.874	10.294	7.259 to 13.329	0.424	13.79	11.882 to 15.698	0.775
	Chemotherapy	13.02	11.514 to 14.527		11.796	9.710 to 13.881		14.208	12.071 to 16.344	
	No endocr. therapy	9.078	6.500 to 11.656	0.001	8.732	4.448 to 13.016	0.197	9.259	6.051 to 12.466	0.001
	Endocrine therapy	13.799	12.581 to 15.018		11.809	9.933 to 13.686		15.128	13.543 to 16.714	
Dyspnea	No chemotherapy	5.712	4.143 to 7.280	<0.001	6.23	3.337 to 9.123	0.03	5.516	3.644 to 7.389	0.011
	Chemotherapy	9.634	8.176 to 11.092		10.125	8.138 to 12.113		9.144	7.050 to 11.237	
	No endocr. therapy	7.219	4.717 to 9.721	0.605	7.695	3.612 to 11.778	0.536	6.963	3.809 to 10.117	0.909
	Endocrine therapy	7.949	6.767 to 9.131		9.103	7.313 to 10.894		7.169	5.611 to 8.727	
Insomnia	No chemotherapy	−0.612	−2.872 to 1.647	0.355	−4.833	−9.165 to −0.502	0.185	0.951	−1.681 to 3.582	0.058
	Chemotherapy	−2.067	−4.165 to 0.031		−1.281	−4.256 to 1.694		−2.856	−5.793 to 0.080	
	No endocr. therapy	−5.477	−9.068 to −1.886	0.014	−7.192	−13.309 to −1.074	0.095	−4.623	−9.031 to −0.215	0.054
	Endocrine therapy	−0.478	−2.178 to 1.223		−1.506	−4.183 to 1.170		0.21	−1.978 to 2.398	
Appetite Loss	No chemotherapy	−4.044	−5.475 to −2.614	<0.001	−9.294	−12.200 to −6.388	0.175	−2.102	−3.696 to −0.509	0.009
	Chemotherapy	−8.485	−9.817 to −7.153		−11.736	−13.734 to −9.738		−5.293	−7.078 to −3.508	
	No endocr. therapy	−7.356	−9.639 to −5.073	0.375	−11.378	−15.482 to −7.274	0.824	−5.248	−7.929 to −2.567	0.158
	Endocrine therapy	−6.214	−7.294 to −5.134		−10.871	−12.669 to −9.073		−3.094	−4.421 to −1.767	
Constipation	No chemotherapy	5.637	3.915 to 7.359	0.468	7.676	4.531 to 10.821	0.959	4.888	2.817 to 6.959	0.81
	Chemotherapy	6.508	4.904 to 8.111		7.776	5.618 to 9.935		5.269	2.949 to 7.589	
	No endocr. therapy	4.299	1.543 to 7.055	0.156	3.694	−0.756 to 8.144	0.052	4.621	1.122 to 8.119	0.785
	Endocrine therapy	6.503	5.206 to 7.800		8.514	6.574 to 10.454		5.162	3.440 to 6.884	
Financial difficulties	No chemotherapy	0.394	−0.843 to 1.631	0.015	1.382	−1.334 to 4.098	0.045	0.031	−1.251 to 1.313	0.833
	Chemotherapy	2.493	1.335 to 3.650		4.759	2.882 to 6.636		0.239	−1.203 to 1.680	
	No endocr. therapy	1.123	−0.865 to 3.111	0.671	3.262	−0.611 to 7.135	0.823	0.009	−2.161 to 2.180	0.909
	Endocrine therapy	1.599	0.665 to 2.534		3.744	2.059 to 5.430		0.150	−0.917 to 1.217	
Diarrhea	No chemotherapy	0.951	−0.342 to 2.245	0.091	−1.619	−4.076 to 0.837	0.555	1.895	0.376 to 3.414	0.629
	Chemotherapy	−0.57	−1.772 to 0.632		−2.517	−4.204 to −0.831		1.334	−0.364 to 3.032	
	No endocr. therapy	−1.136	−3.202 to 0.931	0.183	−2.972	−6.449 to 0.505	0.648	−0.187	−2.747 to 2.373	0.118
	Endocrine therapy	0.417	−0.557 to 1.390		−2.088	−3.606 to −0.571		2.091	0.829 to 3.352	
EORTC BR23, functional scales										
Sexual enjoyment[a]	No chemotherapy	−4.575	−7.354 to −1.796	0.124	−1.717	−6.113 to 2.679	0.055	−6.605	−10.138 to −3.072	0.527
	Chemotherapy	−7.42	−9.756 to −5.084		−6.943	−9.961 to −3.924		−8.252	−11.935 to −4.569	
	No endocr. therapy	−5.994	−10.038 to −1.950	0.893	−3.855	−9.950 to 2.241	0.618	−7.956	−13.291 to −2.622	0.814
	Endocrine therapy	−6.303	−8.298 to −4.308		−5.553	−8.282 to −2.823		−7.228	−10.132 to −4.324	

Continued

Table 2. *Continued*

Symptom, dimension or scale	Treatment	Overall cohort			Premenopausal			Postmenopausal		
		MLS change	95% CI	*P*-value	MLS change	95% CI	*P*-value	MLS change	95% CI	*P*-value
Future perspective	No chemotherapy	11.476	9.513 to 13.439	0.625	12.645	8.775 to 16.514	0.945	11.024	8.771 to 13.276	0.657
	Chemotherapy	12.144	10.324 to 13.965		12.48	9.828 to 15.132		11.789	9.278 to 14.300	
	No endocr. therapy	12.575	9.441 to 15.708	0.609	12.654	7.178 to 18.130	0.962	12.507	8.715 to 16.299	0.511
	Endocrine therapy	11.671	10.196 to 13.147		12.51	10.124 to 14.896		11.087	9.218 to 12.957	
Body image	No chemotherapy	−8.173	−9.712 to −6.635	<0.001	−9.087	−12.240 to −5.934	<0.001	−7.833	−9.545 to -6.122	<0.001
	Chemotherapy	−15.243	−16.669 to −13.817		−17.813	−19.975 to −15.652		−12.705	−14.612 to −10.798	
	No endocr. therapy	−11.645	−14.108 to −9.183	0.771	−13.649	−18.126 to −9.173	0.511	−10.565	−13.451 to −7.678	0.673
	Endocrine therapy	−12.049	−13.209 to −10.889		−15.285	−17.238 to −13.332		−9.872	−11.295 to −8.449	
Sexual functioning	No chemotherapy	0.603	−1.068 to 2.273	0.253	3.277	−0.110 to 6.664	0.262	−0.419	−2.262 to 1.423	0.152
	Chemotherapy	−0.725	−2.269 to 0.819		0.929	−1.389 to 3.248		−2.438	−4.495 to −0.381	
	No endocr. therapy	0.886	−1.758 to 3.530	0.412	0.376	−4.377 to 5.129	0.558	1.152	−1.929 to 4.233	0.079
	Endocrine therapy	−0.338	−1.594 to 0.917		1.93	−0.160 to 4.020		−1.929	−3.462 to −0.397	
EORTC BR23, symptoms scales										
Systemic therapy side-effects	No chemotherapy	6.57	5.710 to 7.430	0.157	8.195	6.571 to 9.818	0.474	5.973	4.962 to 6.984	0.977
	Chemotherapy	7.418	6.617 to 8.219		8.915	7.800 to 10.029		5.951	4.819 to 7.082	
	No endocr. therapy	4.617	3.245 to 5.988	<0.001	6.356	4.063 to 8.650	0.03	3.713	2.013 to 5.412	0.004
	Endocrine therapy	7.561	6.913 to 8.209		9.128	8.126 to 10.130		6.513	5.673 to 7.353	
Breast symptoms	No chemotherapy	8.109	6.923 to 9.295	<0.001	9.735	7.344 to 12.126	0.001	7.499	6.161 to 8.836	0.040
	Chemotherapy	5.128	4.027 to 6.229		4.844	3.208 to 6.480		5.399	3.902 to 6.896	
	No endocr. therapy	4.533	2.642 to 6.425	0.024	4.038	0.681 to 7.396	0.131	4.822	2.563 to 7.082	0.092
	Endocrine therapy	6.947	6.054 to 7.840		6.862	5.384 to 8.340		6.99	5.878 to 8.101	
Arm symptoms	No chemotherapy	9.144	7.552 to 10.737	0.065	8.742	5.638 to 11.846	0.069	9.302	7.465 to 11.139	0.550
	Chemotherapy	11.192	9.714 to 12.669		12.229	10.106 to 14.351		10.143	8.091 to 12.196	
	No endocr. therapy	8.544	6.008 to 11.081	0.146	10.398	6.022 to 14.774	0.725	7.505	4.417 to 10.594	0.124
	Endocrine therapy	10.624	9.426 to 11.822		11.255	9.342 to 13.169		10.207	8.680 to 11.733	
Upset by hair loss[b]	No chemotherapy	7.286	1.451 to 13.122	0.100	8.075	−3.305 to 19.455	0.208	6.822	0.145 to 13.499	0.250
	Chemotherapy	14.377	8.236 to 20.519		17.383	8.364 to 26.401		13.207	4.598 to 21.816	
	No endocr. therapy	9.924	−0.275 to 20.123	0.878	7.839	−10.677 to 26.354	0.495	11.017	−1.114 to 23.148	0.747
	Endocrine therapy	10.801	6.139 to 15.462		14.817	7.142 to 22.492		8.796	2.919 to 14.672	

P-value highlights the *P*-value of the interaction test between receipt of chemotherapy or endocrine therapy and time.

Models include as covariates: age, Charlson's comorbidity index, BMI, smoking, marital status, education level, income, disease staging center volume, type of surgery, axillary management, receipt of trastuzumab, receipt of radiotherapy, presence of anxiety and presence of depression, all of which collected at diagnosis.

[a]Denote that question was only to be answered if patients stated to have been sexually active or ([b]) if patients stated they had experienced hair loss, resulting in fewer patients responding to these questions compared with other questions.

CI, confidence interval; Endocr., endocrine; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; MLS, Mean least square.

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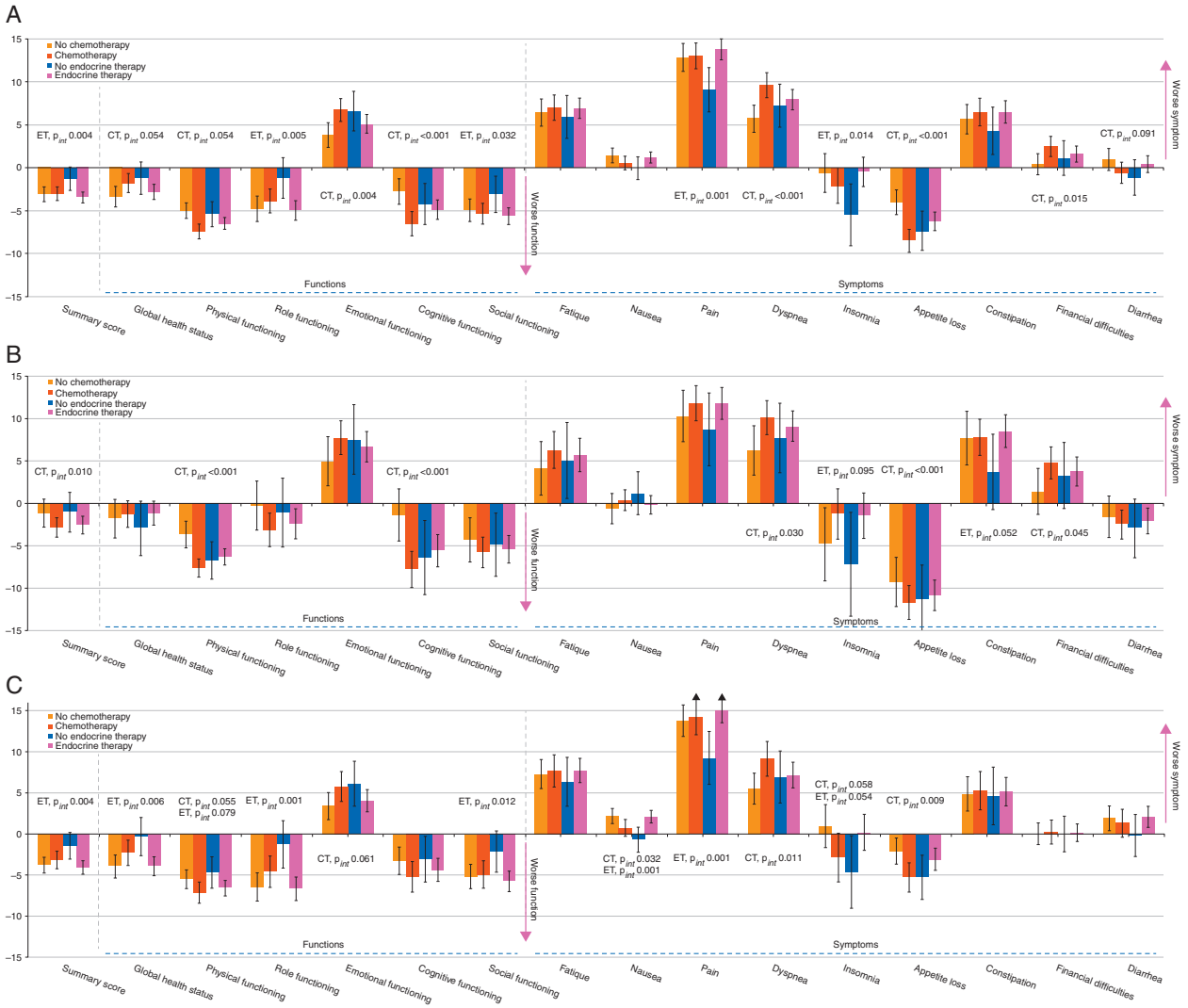

Figure 2. Mean least square change of European Organization for Research and Treatment of Cancer QLQ C30 PRO domains score from diagnosis to the '2 years after diagnosis visit' in patients treated and not treated with chemotherapy or endocrine therapy in the overall cohort (A), and in premenopausal (B) and postmenopausal (C) patients. Error bars refer to the 95% confidence interval of the estimate. *P*-values refer to the interaction (P_{int}) of the treatment with chemotherapy or endocrine therapy and time. Only *P*-values <0.1 are shown. Estimates and confidence intervals derived from multivariate generalized estimating equations models.

differential effect of treatment classes by menopausal status on QoL should be considered when discussing optimal adjuvant therapy options and survivorship care as they may have implications for adherence and long-term health and psychosocial outcomes. While systemic treatment is a major driver in QoL, we recognize that the optimal support is a continuum that must consider, among others, the psychological disruption of cancer diagnosis and the sequelae of local interventions. Our data challenge the common idea that ET is an innocent player in the QoL arena and highlight that appropriate selection of women for ET treatment escalation should be a research priority.

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