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RESEARCH

Pooled analysis of NeoCARH and NeoCART trials: patient-reported outcomes in patients with early-stage breast cancer receiving platinum-based or anthracycline-based neoadjuvant chemotherapy

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Abstract

Purpose Anthracycline-based or platinum-based neoadjuvant chemotherapy belongs to the standard treatment for early-stage breast cancer (EBC) that is either triple-negative or human epidermal growth factor receptor 2 positive (HER2 +). Currently, there is a paucity of data comparing their impact on health-related quality of life (HRQoL).

Methods Triple-negative or HER2 + EBC from our two prospective randomized controlled trials, neoCARH and neoCART, were divided into two groups based on the neoadjuvant chemotherapy regimens they received: anthracycline-based or platinum-based group. HRQoL was the exploratory endpoint in these two trials, which was assessed using the European Organization for Research and Treatment of Cancer Quality of Life-Core30 and Breast23 questionnaires. The primary variable of interest was the C30 summary score (C30-SumSc). Assessments were carried out at baseline, after neoadjuvant chemotherapy, and 1 year and 2 years after diagnosis.

Results The mean questionnaires' compliance rate was 95.0%. After neoadjuvant chemotherapy, 210 patients had evaluable HRQoL data, the mean least square change from baseline for the platinum-based group was − 15.997 (95% confidence interval (CI): − 17.877 to − 14.117), and it was − 20.156 (95% CI: − 22.053 to − 18.258) for the anthracycline-based group (difference: 4.159, 95% CI: 1.462 to 6.855, $P = 0.003$, minimal important difference = 3). For the majority of the domains of interest assessed by the C30 and BR23 questionnaires, the platinum-based group demonstrated superior outcomes in comparison to the anthracycline-based group.

Conclusion Patients receiving platinum-based or anthracycline-based regimens both experienced worsened HRQoL after neoadjuvant chemotherapy; however, the former provided relatively better HRQoL compared with the latter.

Clinical trial registration: ClinicalTrials.gov: NCT03140553. Registered 4 May 2017 (neoCARH). NCT03154749. Registered 16 May 2017 (neoCART).

Keywords Early-stage breast cancer · Neoadjuvant chemotherapy · Platinum agents · Anthracycline agents · Patient-reported outcomes · Quality of life

Introduction

For patients diagnosed with triple-negative or human epidermal growth factor receptor 2 positive (HER2 +) breast cancer, anthracycline-based neoadjuvant chemotherapy is considered one of the standard treatment options. Despite being effective, the use of anthracycline is limited due to its noticeable cardiotoxicity [1, 2]. As a result, researchers have been exploring anthracycline-sparing regimens. Previous studies have shown that adding platinum to anthracycline-based regimens or using platinum-based regimens can increase these patients' pathological complete

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response (pCR) rate compared to anthracycline-based regimens [3, 4].

In our center, consistent results were obtained from two prospective randomized controlled trials, neoCARH and neoCART [5, 6]. In the neoCARH trial, patients with HER2 + early-stage breast cancer (EBC) achieved a higher pCR rate with the neoadjuvant TCbH regimen compared to the EC-TH regimen (55.9% versus (vs) 37.3%, $P = 0.032$). Similarly, the neoCART trial found that the neoadjuvant TCb regimen resulted in a higher pCR rate than the EC-T regimen in patients with triple-negative EBC (61.4% vs 38.6%, $P = 0.004$). The management of treatment-related adverse events (AEs) in patients receiving platinum-based regimens was also found to be acceptable compared to anthracycline-based regimens. Considering these positive findings, the National Comprehensive Cancer Network (NCCN) guidelines currently still endorse the results of the neoCART trial [7].

However, treatment-related AEs are objective measures that are evaluated by clinicians or researchers, and there is a lack of subjective feedback directly from patients. Patient-reported outcomes (PROs) provide direct reports from patients about their health status and treatment-related experiences without modification by clinicians or others [8, 9]. The Food and Drug Administration (FDA) recognizes the potential value of core PROs data in the benefit-risk assessment of anticancer drugs and has incorporated PROs as evidence for drug approval [10–12]. Moreover, numerous trials, such as Destiny-Breast03, SOLTI CORALLEEN, ASCENT, KEYNOTE-407, and so on, have integrated PROs as secondary or exploratory endpoints to enhance patients' quality of life (QoL) while ensuring the efficacy of anticancer drugs [13–21].

The number of breast cancer survivors is increasing, with a 5-year survival rate of over 90% for early-stage patients [22]. Both the American Society of Clinical Oncology (ASCO) Breast Cancer Survivorship Care Guidelines and the European Society for Medical Oncology (ESMO) Cancer Survivorship Expert Consensus emphasize the importance of assessing the long-term impact of treatment on patients' physical, psychosocial, and social functioning, to provide high-quality care and improve their long-term QoL [23, 24]. Hence, it is crucial to evaluate PROs following treatment.

In this study, we present the health-related quality of life (HRQoL) data collected from the neoCARH and neoCART trials. Our primary objective was to compare the HRQoL differences between neoadjuvant chemotherapy regimens of platinum-based (TCb or TCbH) and anthracycline-based (EC-T or EC-TH) among patients diagnosed with triple-negative or HER2 + EBC during (post-neoadjuvant chemotherapy) and after (1-year, 2-year post-diagnosis) primary treatment.

Materials and methods

Study design

The neoCARH (ClinicalTrials.gov NCT03140553) and neoCART (ClinicalTrials.gov NCT03154749) are randomized control, multicenter, phase II trials conducted in our center. In the neoCARH trial, patients with clinical stage II–IIIC HER2 + breast cancer were randomized in a 1:1 ratio to either the EC-TH group, which involved four cycles of intravenous epirubicin (90 mg/m^2) and cyclophosphamide followed by four cycles of docetaxel and trastuzumab every 3 weeks, or the TCbH group, which consisted of six cycles of docetaxel plus carboplatin (area under the curve, 6 mg/ml per min) administered every 3 weeks concurrently with trastuzumab. Similarly, in the neoCART trial, patients with clinical stage II–III triple-negative breast cancer were randomly assigned in a 1:1 ratio to either the experimental TCb (carboplatin, area under the curve, 6 mg/ml per min) group or the EC-T (epirubicin, 90 mg/m^2) group. The primary endpoint for both trials is the pCR rate. Previous publications have provided detailed information about these trials [5, 6]. In this study, patients were categorized into the anthracycline-based group (EC-T or EC-TH) or the platinum-based group (TCb or TCbH) based on the regimens they received.

The Research Ethics Committee of the Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences approved both of these trials, and the protocols underwent review by the respective ethics committees at each center. Both trials were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, and all participants provided written informed consent.

Prespecified exploratory endpoint

HRQoL is a prespecified exploratory endpoint in the neoCARH and neoCART trials. The assessment time points for HRQoL include T0 (baseline), T1 (1 week after the last dose of neoadjuvant chemotherapy), T2 (1 year after diagnosis), and T3 (2 years after diagnosis). HRQoL assessments utilize the validated and widely used European Organization for Research and Treatment of Cancer Quality of Life-Core30 (EORTC QLQ-C30) questionnaire (oncology-specific), along with the EORTC QLQ-Breast23 (BR23) questionnaire (breast cancer-specific). The C30 questionnaire consists of 30 items arranged into 15 domains: a 2-item global health status (GHS)/QoL domain, 5 multi-item functioning domains, 3 multi-item

symptom domains, and 6 single-item symptom domains [25]. Similarly, the BR23 questionnaire consists of 23 items arranged into 8 domains: 4 multi-item functioning domains and 4 multi-item symptom domains [26]. The questionnaires were scored according to the scoring manuals of EORTC QLQ-C30 and BR23 [27, 28]. The C30 summary score (C30-SumSc) was calculated by taking the mean of the scores from the 13 domains, except for the GHS/QoL and financial difficulties domains (the scores from the symptom domains were reversed before calculation) [29]. For the C30-SumSc, GHS/QoL, and functioning domains, scores ranged from 0 to 100; higher scores indicate better HRQoL. Scores for the symptom domains also ranged from 0 to 100, but higher scores indicate worse symptomatology. The primary variable of interest is the C30-SumSc [29]. Secondary variables of interest include GHS/QoL, physical functioning, role functioning, emotional functioning, social functioning, fatigue, pain, diarrhea, constipation, appetite loss, and systemic therapy side effects of the C30 and BR23 questionnaires. These variables were chosen based on their relationship with typical drug-related AEs, their inclusion as core PROs data that the FDA advises collecting, or their identification as important PRO domains [5, 6, 10, 30].

The left ventricular ejection fraction (LVEF) evaluation

LVEF of patients was evaluated through color Doppler echocardiography at baseline and after neoadjuvant chemotherapy.

Statistical analyses

The statistical analysis was conducted using Statistical Product and Service Solutions version 26.0 (SPSS 26.0). The GraphPad Prism 8 was used to create the figures. The mean least squares (MLS) changes from baseline and between-group differences in MLS change from baseline for the scores of the C30 and BR23 questionnaires were calculated using linear mixed-effect models for repeated measures (MMRM). The model considered groups (the platinum-based group and the anthracycline-based group), time points (modeled as a categorical variable, including T0, T1, T2, and T3), baseline score, the interaction between baseline score and time points, and the interaction between groups and time points as fixed effects. Only patients who had HRQoL data at baseline and at least one subsequent time point were included in the analysis. The definition of completion rate is the percentage of patients who complete more than half of the items in each domain of the EPRTC QLQ-C30 questionnaire and ≥ 1 item of the EPRTC QLQ-BR23 questionnaire at each time point out of the number of patients randomized. The compliance rate was defined as the percentage of patients who complete more than half of the items in each domain of the EPRTC QLQ-C30 questionnaire and ≥ 1 item of the EPRTC QLQ-BR23 questionnaire at each time point over the number of patients who were expected to complete the HRQoL assessment, excluding patients who were missing by design (i.e., death, discontinuation). In the C30 and BR23 domains, the absolute value of the MLS changes from baseline of ≥ 10 points was deemed clinically relevant [31]. Furthermore, referring to a previous study [19], the absolute value of the difference in MLS changes from baseline (MLSCFB) between groups was considered clinically significant if it exceeded the minimal important difference (MID) derived from evidence-based guidelines for the C30 questionnaire [32], or calculated as 0.3 × standard deviation for the mean change score between baseline and a subsequent evaluation time point [33]. Missing data for C30 and BR23 questionnaires' scores were analyzed using multiple imputations. In parallel, the chi-squared test or Fisher's exact test was employed for categorical variables, while the two-sample *t* test or Mann–Whitney *U* test was utilized for continuous variables. To deal with the clustering effect of the neoCARH and neoCART tests, we carried out the following sensitivity analysis. First, the two trials were taken as stratified factors and incorporated into the linear mixed-effect model as random effects. Second, the two trials were analyzed as subgroups respectively. In the sensitivity analysis, we only focus on the primary variable of interest, namely the C30-SumSc. Since HRQoL was not included in the hierarchical testing plan for the neoCARH or neoCART trials, the reported *P* values are considered nominal, and there was not adjusted for multiple comparisons. All tests were conducted using a two-sided approach with 95% confidence interval (CI). A significance level of < 0.05 was deemed statistically significant.

Results

Baseline characteristics

The process by which patients were enrolled in this study is depicted in Fig. 1. From September 1, 2016, to December 31, 2019, a total of 223 patients from 9 centers were randomly assigned to either the anthracycline-based group ($n = 111$) or the platinum-based group ($n = 112$). Table 1 demonstrates that the baseline characteristics of patients were well-balanced between the two groups.

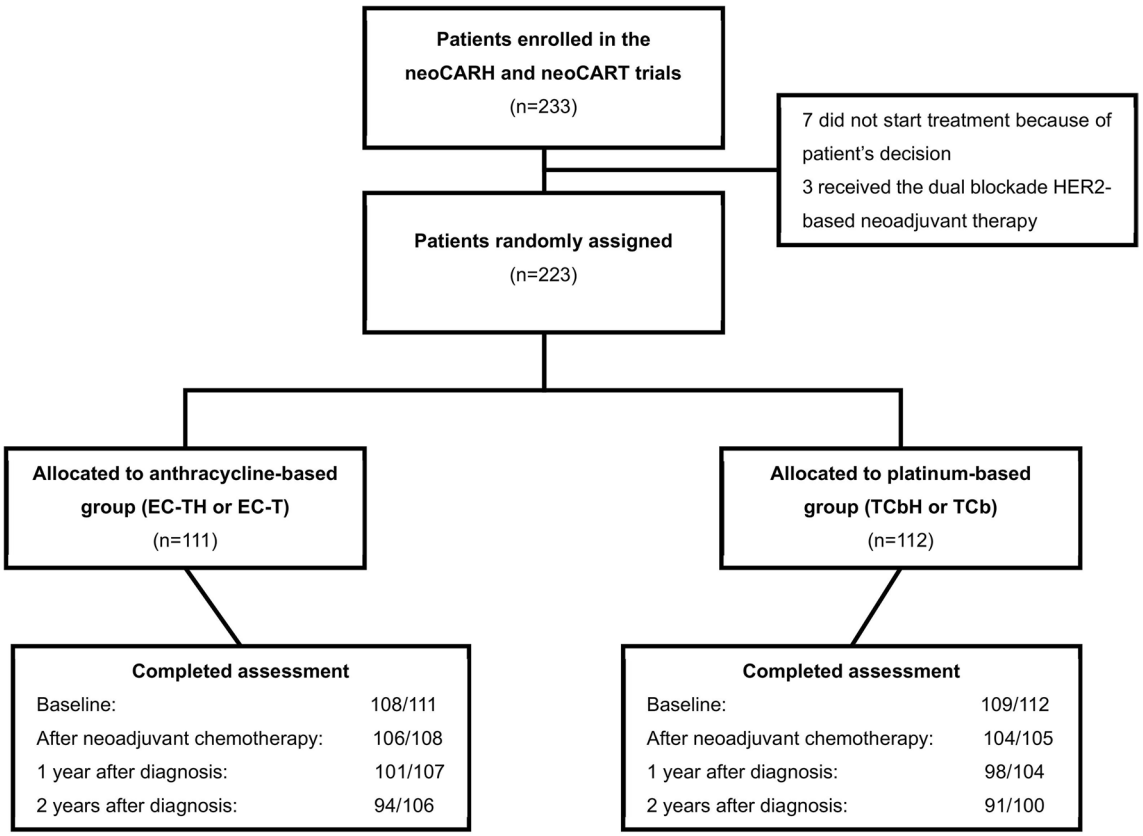

Fig. 1 Flow diagram for patients enrolled in this HRQoL study. Abbreviation. HRQoL, health-related quality of life; HER2, human epidermal growth factor receptor 2; EC-TH, four cycles of epirubicin and cyclophosphamide, followed by four cycles of docetaxel and trastuzumab every 3 weeks; EC-T, four cycles of epirubicin and cyclophosphamide, followed by four cycles of docetaxel; TCbH, docetaxel, carboplatin, plus trastuzumab administered every 3 weeks for six cycles; TCb, docetaxel plus carboplatin administered every 3 weeks for six cycles

Completion rate, compliance rate, and baseline score of questionnaires

The average completion rate of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires across all follow-up periods was 90.9%. Specifically, the completion rates were 97.3% at baseline (217/223), 94.2% after neoadjuvant chemotherapy (210/223), 89.2% 1 year after diagnosis (199 /223), and 83.0% 2 years after diagnosis (185/223). The average compliance rate across all follow-up periods was 95%, including 97.3% at baseline (217/223), 98.6% after neoadjuvant chemotherapy (210/213), 94.3% (199/211) 1 year after diagnosis, and 89.8% (185/206) 2 years after diagnosis. There were no statistical differences in the C30-SumSc and the majority of domain scores in the C30 and BR23 questionnaires at baseline between the two groups (Table S1).

Primary variable of interest

The calculated MLSCFB for post-neoadjuvant chemotherapy in the C30-SumSc for the platinum-based group was − 15.997 (95%CI: − 17.877 to − 14.117) and for the anthracycline-based group was − 20.156 (95%CI: − 22.053 to − 18.258). The difference between the two groups was found to be 4.159 (95%CI: 1.462 to 6.855, $P = 0.003$, MID = 3), indicating both statistically and clinically better HRQoL related to the platinum-based group (Fig. 2 and Table S2). During the 1-year and 2-year follow-ups post-diagnosis, the C30-SumSc gradually returned to the baseline level, and no statistical differences were observed between the two groups.

Table 1 Baseline characteristics of all patients and patients in the anthracycline-based or platinum-based group

	All patients $N=223$	Anthracycline-based group[a] $n=111$	Platinum-based group[b] $n=112$	*P* value
Age, years				0.191
Median (SD)	50.2 (8.2)	49.6 (7.5)	50.8 (8.9)	
BMI, WHO definition, kg/m^2				0.987
Mean (SD)	23.7 (2.9)	23.8 (3.1)	23.7 (2.7)	
Marital status, *n* (%)				0.617
Living alone	16 (7.2)	7 (6.3)	9 (8.0)	
Living as couple	207 (92.8)	104 (93.7)	103 (92.0)	
Menopausal status, *n* (%)				0.838
Premenopausal	117 (52.5)	59 (53.2)	58 (51.8)	
Postmenopausal	106 (47.5)	52 (46.8)	54 (48.2)	
Smoking status, *n* (%)				0.119
Former smoker	6 (2.7)	5 (4.5)	1 (0.9)	
Never smoker	217 (97.3)	106 (95.5)	111 (99.1)	
Alcohol consumption status, *n* (%)				0.682
Less than daily	191 (85.7)	94 (84.7)	97 (86.6)	
Never	32 (14.3)	17 (15.3)	15 (13.4)	
Education, *n* (%)				0.834
Primary school	57 (25.7)	30 (27.0)	27 (24.1)	
High school	43 (19.3)	23 (20.7)	20 (17.9)	
College or higher	96 (43.0)	46 (41.4)	50 (44.6)	
Missing	27 (12.1)	12 (10.8)	15 (13.4)	
Clinical TNM stage, *n* (%)				0.803
II	157 (70.4)	79 (71.2)	78 (69.6)	
III	66 (29.6)	32 (28.8)	34 (30.4)	
IHC-defined subtype of breast cancer, *n* (%)				1.000
HR + /HER2 +	68 (30.5)	34 (30.6)	34 (30.4)	
HR − /HER2 +	67 (30.0)	33 (29.7)	34 (30.4)	
HR − /HER2 −	88 (39.5)	44 (39.6)	44 (39.3)	
Surgery type, *n* (%)				0.212
Mastectomy	152 (68.2)	80 (72.1)	72 (64.3)	
BCS	71 (31.8)	31 (27.9)	40 (35.7)	
Axillary management, *n* (%)				0.256
Sentinel node	121 (54.3)	56 (50.5)	65 (58.0)	
Axillary dissection	102 (45.7)	55 (49.5)	47 (42.0)	
Adjuvant chemotherapy, *n* (%)				0.060
No	218 (97.8)	111 (100.0)	107 (95.5)	
Yes	5 (2.2)	0	5 (4.5)	
Endocrine therapy, *n* (%)				0.797
No	161 (72.2)	81 (73.0)	80 (71.4)	
Yes	62 (27.8)	30 (27.0)	32 (28.6)	
HER2-directed therapy, *n* (%)				0.957
No	88 (39.5)	44 (39.6)	44 (39.3)	
Yes	135 (60.5)	67 (60.4)	68 (60.7)	
Radiotherapy, *n* (%)				0.602
No	74 (33.2)	35 (31.5)	39 (34.8)	
Yes	149 (66.8)	76 (68.5)	73 (65.2)	

SD standard deviation, *BMI* body mass index, *WHO* World Health Organization, *TNM* Tumor Node Metastasis, *IHC* immunohistochemistry, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *BCS* breast-conserving surgery

[a]The chemotherapy regimens of the anthracycline-based group were EC-TH (four cycles of epirubicin and cyclophosphamide, followed by four cycles of docetaxel and trastuzumab every 3 weeks) in 60.4% of patients or EC-T (four cycles of epirubicin and cyclophosphamide, followed by four cycles of docetaxel) in 39.6% of patients

Table 1 (continued)

[b]The neoadjuvant chemotherapy regimens of the platinum-based group were TCbH (docetaxel, carboplatin, plus trastuzumab administered every 3 weeks for six cycles) in 60.7% of patients or TCb (docetaxel plus carboplatin administered every 3 weeks for six cycles) in 39.3% of patients

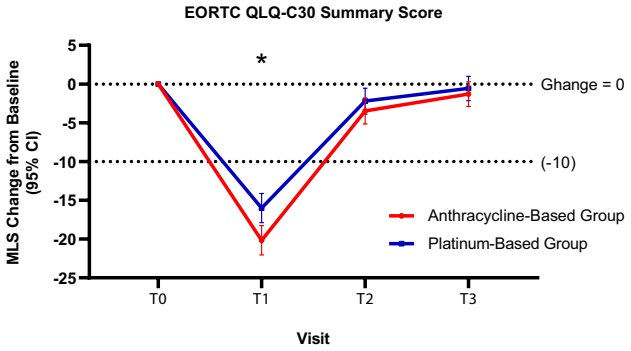

Fig. 2 MLS change from baseline for EORTC QLQ-C30 summary score. EORTC QLQ-C30 summary score range from 0 to 100, a higher score represents better quality of life. Data are from a mixed-effect model for repeated measures analysis. *, $P<0.05$ (platinum-based group versus anthracycline-based group). Abbreviation: MLS, mean least square; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; CI, confidence interval; T0, baseline; T1, 1 week after the last dose of neoadjuvant chemotherapy; T2, 1 year after diagnosis; T3, 2 years after diagnosis

Secondary variables of interest

In terms of functional domains, the platinum-based group had statistically and clinically better physical functioning (difference in MLSCFB: after neoadjuvant chemotherapy: 7.093, 95%CI: 1.664 to 12.522, $P=0.011$, MID = 5; 1 year after diagnosis: 5.385, 95%CI: 0.030 to 10.739, $P=0.049$, MID = 5) and role functioning (difference in MLSCFB: after neoadjuvant chemotherapy: 12.405, 95% CI: 6.672 to 18.138, $P<0.001$, MID = 6; 1 year after diagnosis: 7.912, 95% CI: 2.015 to 13.808, $P=0.009$, MID = 6) compared to the anthracycline-based group. Statistically and clinically significant better social functioning was observed after neoadjuvant chemotherapy for the platinum-based group compared to the anthracycline-based group (difference in MLSCFB: 14.483, 95% CI: 8.853 to 20.113, $P<0.001$, MID = 5). Additionally, statistical improvement in emotional functioning in the platinum-based group compared to the anthracycline-based group could be seen 1 year (difference in MLSCFB: 6.719, 95% CI: 2.235 to 11.202, $P=0.003$, MID = 7) and 2 years after diagnosis (difference in MLSCFB: 5.419, 95% CI: 0.729 to 10.109, $P=0.024$, MID = 8) (Fig. 3 and Table S2).

In terms of symptom domains, patients in the platinum-based group exhibited significantly less fatigue both statistically and clinically after neoadjuvant chemotherapy, in comparison to the anthracycline-based group (difference in MLSCFB: −17.846, 95% CI: −25.445 to −10.247, $P<0.001$, MID = 5). Furthermore, it has been consistently observed that the platinum-based regimens result in lower levels of pain at all follow-up time points in comparison to the anthracycline-based group. These differences between the two groups are statistically significant and also hold clinical significance. Overall, patients in the platinum-based group reported statistically fewer side effects from systemic therapy 1-year post-diagnosis compared to the anthracycline-based group (difference in MLSCFB: −6.084, 95% CI: −11.734 to −0.434, $P=0.035$, MID = 7). Nevertheless, patients in the platinum-based group experienced statistically and clinically more severe constipation 1-year post-diagnosis when compared to the anthracycline-based group (difference in MLSCFB: 8.457, 95% CI: 2.753 to 14.160, $P=0.004$, MID = 5). Additionally, the platinum-based group exhibited more statistically significant appetite loss at 2 years post-diagnosis compared to the anthracycline-based group (difference in MLSCFB: 4.055, 95% CI: 0.556 to 7.554, $P=0.023$, MID = 5) (Fig. 4 and Table S2).

LVEF

Up until the completion of the neoadjuvant chemotherapy, LVEF data was available for a total of 92.8% (207/223) of the patients. Both groups exhibited high levels of LVEF both at the baseline and after completing the neoadjuvant chemotherapy, with an average LVEF greater than 66%. Additionally, there were no statistical differences in LVEF observed between the two groups (Table 2).

Sensitivity analyses for the clustering effects of the neoCARH and neoCART trials

The results of the sensitivity analyses, presented in Table S3, were generally consistent with those of the primary analysis. Specifically, HRQoL was significantly impaired in both the platinum-based and anthracycline-based treatment groups after neoadjuvant chemotherapy. However, the HRQoL of the platinum-based group was relatively better than the anthracycline-based group. Over time, the HRQoL of both groups gradually returned to baseline levels at 1 and 2 years after diagnosis, with no significant difference between the groups.

Discussion

Analysis of the HRQoL data from the neoCARH and neoCART trials [5, 6] revealed that after neoadjuvant chemotherapy, the platinum-based regimens outperformed the

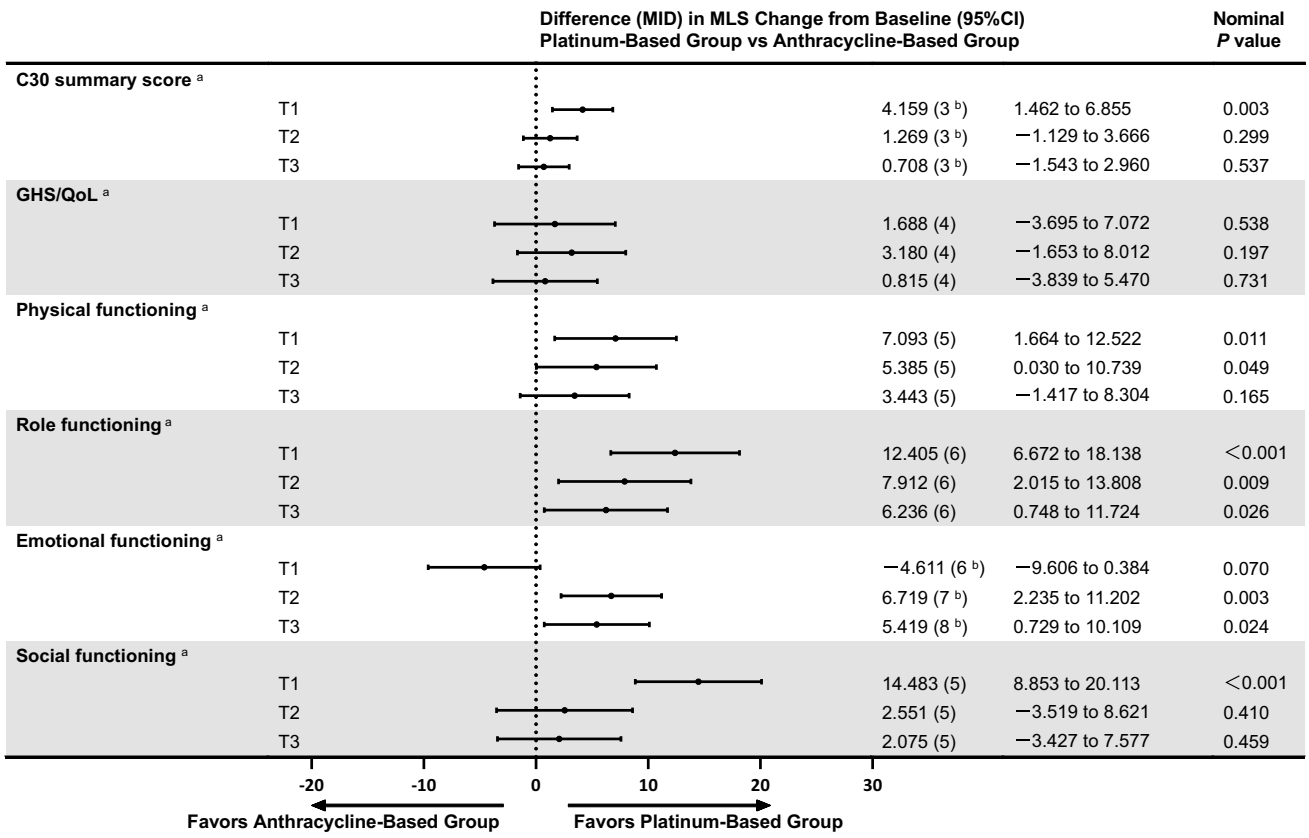

Fig. 3 Forest plots of MLS difference between groups for focused EORTC QLQ-C30 domains' scores. [a]Range from 0 to 100, a higher score represents better quality of life or functioning. [b]For the EORTC QLQ-C30 summary score and emotional functioning, the MID was derived as 0.3 × SD for the mean change score between two visits. Abbreviation: MLS, mean least square; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; GHS, global health status; QoL, quality of life; MID, minimal important difference; CI, confidence interval; T1, 1 week after the last dose of neoadjuvant chemotherapy; T2, 1 year after diagnosis; T3, 2 years after diagnosis; SD, standard deviation

anthracycline-based regimens in various domains of the EORTC QLQ-C30 questionnaire including the C30-SumSc, physical functioning, role functioning, social functioning, fatigue, and pain, showing that the platinum-based regimens are related to a better HRQoL compared to the anthracycline-based regimens.

Although AEs related to the neoCARH and neoCART trials have been reported, these are objective indicators assessed by clinicians or researchers. It is important to note that toxicities associated with anticancer therapies, especially subjective symptoms like fatigue and pain, are often overlooked or underestimated by clinicians. However, this information is crucial in clinical practice [34, 35]. At this moment, there is an urgent need for PROs. Including PROs in clinical practice promotes effective communication between patients and clinicians, facilitating early detection and intervention for treatment-related symptoms [34, 36]. Studies have shown that the use of PROs can lead to a reduction in emergency visits and hospitalizations, as well as improvements in symptoms, physical functioning, quality of life, treatment adherence, and overall survival [37–40]. Furthermore, this information has already been incorporated into the labeling claims of drugs by the FDA, providing supportive evidence for drug approval [11, 12, 35]. Additionally, it is worth noting that breast cancer is the most common malignant tumor in women [41, 42], further highlighting the significance of PROs data in this patient population. Various questionnaires are commonly used to assess PROs, with the EORTC QLQ-C30 and BR23/45 frequently employed in clinical trials on breast cancer. Trials such as DestinyBreast03, CANTO, ASCENT, and UK TACT have utilized these two questionnaires to assess PROs [13, 14, 17, 19, 43]. In our study, we are also utilizing these two questionnaires.

C30-SumSc provides a comprehensive summary of the C30 questionnaire. Using it as the primary variable of interest can reduce the risk of Type I errors when comparing repeated measurements using the other 15 domains [29]. Additionally, the C30-SumSc has a stronger predictive value for overall survival compared to the other C30 domains [44]. The PRO study of the CANTO trial used the C30-SumSc as

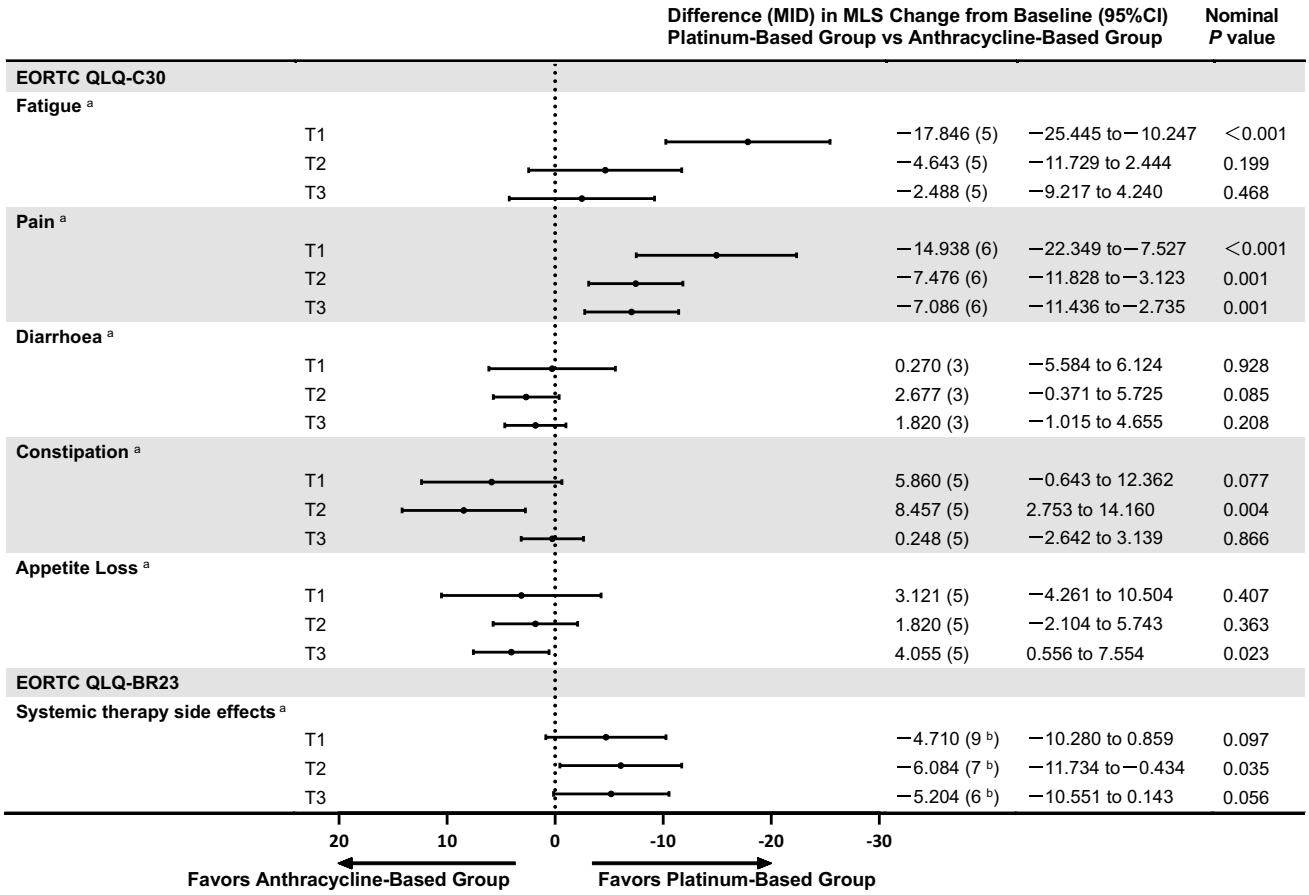

Fig. 4 Forest plots of MLS difference between groups for focused EORTC QLQ-C30 and BR23 domains' scores. [a]Range from 0 to 100, a higher score represents worse symptomatology. [b]For the EORTC QLQ-BR23 systemic therapy side effects, the MID was derived as 0.3 × SD for the mean change score between two visits. Abbreviation: MLS, mean least square; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; BR23, Breast23; MID, minimal important difference; CI, confidence interval; T1, 1 week after the last dose of neoadjuvant chemotherapy; T2, 1 year after diagnosis; T3, 2 years after diagnosis; SD, standard deviation

Table 2 LVEF measurements at T0 and T1 for anthracycline-based or platinum-based group

	Mean LVEF, % (SD)			Platinum-based group versus Anthracycline-based group, *P* value
	All patients *N* = 207	Anthracycline-based group *n* = 102	Platinum-based group *n* = 105	
T0	66.2 (3.3)	66.2 (4.0)	66.3 (2.5)	0.626
T1	66.4 (3.4)	66.3 (3.6)	66.4 (3.2)	0.526

Abbreviation: *LVEF* left ventricular ejection fraction, *T0* baseline, *T1* 1 week after the last dose of neoadjuvant chemotherapy, *SD* standard deviation

its primary endpoint [13, 14]. Similarly, in this study, the C30-SumSc serves as the primary variable of interest. It was found that, after neoadjuvant chemotherapy, patients in the platinum-based group had higher C30-SumSc, which was statistically and clinically significant, in comparison to the anthracycline-based group. However, at 1 year and 2 years after diagnosis, there was no statistical difference in the C30-SumSc between the two groups, and it gradually returned to the baseline level. This finding is consistent with previous studies, which demonstrate that most physical and psychosocial symptoms of treatment typically resolve within the first year after diagnosis, and most breast cancer survivors can regain a higher level of quality of life [45–48].

For the secondary variables of interest, such as fatigue, pain, and systemic therapy side effects, the platinum-based group exhibited better outcomes compared to the anthracycline-based group at various follow-up time points. However, it is important to note that patients in the platinum-based group also experienced more severe constipation or appetite loss at 1 or 2 years after diagnosis. These HRQoL findings align with previous reports of AEs in the neoCARH and neoCART trials [5, 6]. For example, the

incidence rates of fatigue, arthralgia, and bone pain were higher in the anthracycline-based regimens (30.6%, 23.9%, and 43.2%, respectively) compared to the platinum-based regimens (22.3%, 11.8%, and 27.3%, respectively). Similarly, the platinum-based regimens had higher incidence rates of constipation (17%), anorexia (13.2%), and dysgeusia (4.4%) compared to the anthracycline-based regimens (11.7%, 6.8%, and 1.5%, respectively).

The BCIRG 006 trial evaluated the HRQoL in HER2 + breast cancer patients receiving adjuvant chemotherapy using three different treatment regimens: TCbH, AC-T, and AC-TH. The PROs questionnaires utilized in the trial were the EORTC QLQ-C30 and BR23. The findings of the trial indicated that the TCbH group experienced fewer systemic therapy side effects after adjuvant chemotherapy. Overall, there were no statistically significant differences observed in HRQoL among the three regimens [49]. According to our investigation, we also observed that the group receiving platinum-based therapy encountered numerically fewer adverse effects from systemic therapy in comparison to the group receiving anthracycline-based therapy after neoadjuvant chemotherapy.

One of the main AEs associated with anthracyclines is their cardiotoxicity. A study conducted over a median follow-up of 5.2 years observed an incidence rate of 9% for anthracycline-induced cardiotoxicity. The median time to occurrence of this cardiotoxicity was 3.5 months after completion of chemotherapy, with almost all patients (98%) experiencing it within the first year. The incidence rate is positively correlated with the cumulative drug dose, with a rate as high as 36% when the cumulative dose exceeds 601 mg/m^2 [1, 2]. Our study only collected LVEF data at baseline and after neoadjuvant chemotherapy. We found that both the group receiving platinum-based and the group receiving anthracycline-based regimens showed high LVEF (average LVEF all > 66%), with no statistical differences between the two groups. However, a longer follow-up period is required to perform a more precise comparison of cardiotoxicity between anthracyclines and platinum.

This study demonstrates a notable strength in its high questionnaire compliance rate, which is consistently maintained at an average of 95.0%. Moreover, even after a 2-year follow-up period, the compliance rate remains at a commendable 89.8%. Nonetheless, the study does have certain limitations that should be acknowledged. Firstly, both the neoCART and neoCART trials utilize a non-blinded design, and patients' understanding of the treatment assignment may influence their responses to questions on PRO assessments. However, one study has shown that this does not affect patients' responses to the PRO questionnaires [50]. Secondly, the analyses were not adjusted for multiple comparisons.

Conclusions

Our study focused on patients with triple-negative or HER2 + EBC who received neoadjuvant chemotherapy in the neoCARH and neoCART trials. We found that both patients receiving platinum-based or platinum-based regimens experienced worsened HRQoL after neoadjuvant chemotherapy; however, the former provided relatively better HRQoL compared with the latter, which also showed clinically relevant. These results, along with their higher pCR rate and manageable safety profiles as observed in the neoCARH and neoCART trials, provide supporting evidence for the application of platinum-based regimens in clinical practice.

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Author contribution All authors contributed to the project administration, data curation, software, formal analysis, writing—review and editing, and visualization. Ciqiu Yang, Peiyong Li, and Kun Wang contributed to the conceptualization and methodology. Kun Wang contributed to the supervision and funding acquisition. Ciqiu Yang contributed to the funding acquisition. The first draft of the manuscript was written by Ciqiu Yang and Peiyong Li, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences (Date April 20, 2016 for the neoCART trial and April 23 for the neoCARH trial/ No.GDREC 2016420H for the neoCART trial and 2016423H(R1) for the neoCARH trial).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

References

1. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F et al (2015) Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 131:1981–1988. https://doi.org/10.1161/CIRCULATIONAHA.114.013777
2. Singal PK, Iliskovic N (1998) Doxorubicin-induced cardiomyopathy. New England J Med 339:900–905. https://doi.org/10.1056/NEJM199809243391307
3. Poggio F, Bruzzone M, Ceppi M, Pondé NF, La Valle G, Del Mastro L et al (2018) Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol 29:1497–1508. https://doi.org/10.1093/annonc/mdy127
4. Villacampa G, Matikas A, Oliveira M, Prat A, Pascual T, Papakonstantinou A (2023) Landscape of neoadjuvant therapy in HER2-positive breast cancer: a systematic review and network meta-analysis. European J Cancer 2023:112885. https://doi.org/10.1016/j.ejca.2023.03.042
5. Gao H-F, Wu Z, Lin Y, Song X-Y, Cao Y, Chen Q-J et al (2021) Anthracycline-containing *versus* carboplatin-containing neoadjuvant chemotherapy in combination with trastuzumab for HER2-positive breast cancer: the neoCARH phase II randomized clinical trial. Ther Adv Med Oncol 13:175883592110090. https://doi.org/10.1177/17588359211009003
6. Zhang L, Wu Z-Y, Li J, Lin Y, Liu Z, Cao Y et al (2022) Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): Results from a multicenter, randomized controlled, open-label phase II trial. Int J Cancer 150:654–662. https://doi.org/10.1002/ijc.33830
7. National Comprehensive Cancer Network (NCCN) Breast Cancer. Version 4. 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
8. (2006) U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 4:79. https://doi.org/10.1186/1477-7525-4-79
9. Di Maio M, Basch E, Denis F, Fallowfield LJ, Ganz PA, Howell D et al (2022) The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. Ann Oncol 33:878–892. https://doi.org/10.1016/j.annonc.2022.04.007
10. Food and Drug Administration (FDA) Core-patient-reported-outcomes-in-cancer-clinical-trials-guidance-for-industry. Available at: https://www.fda.gov/media/149994/download
11. McKee AE, Farrell AT, Pazdur R, Woodcock J (2010) The role of the U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. The Oncologist 15:13–8. https://doi.org/10.1634/theoncologist.2010-S1-13
12. Hong K, Majercak KR, Villalonga-Olives E, Perfetto EM (2021) Patient-reported outcomes in breast cancer FDA drug labels and review documents. J Patient Rep Outcomes 5:36. https://doi.org/10.1186/s41687-021-00308-y
13. Ferreira AR, Di Meglio A, Pistilli B, Gbenou AS, El-Mouhebb M, Dauchy S et al (2019) Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. Ann Oncol 30:1784–1795. https://doi.org/10.1093/annonc/mdz298
14. Di Meglio A, Havas J, Gbenou AS, Martin E, El-Mouhebb M, Pistilli B et al (2022) Dynamics of long-term patient-reported quality of life and health behaviors after adjuvant breast cancer chemotherapy. JCO 40:3190–3204. https://doi.org/10.1200/JCO.21.00277
15. Schreiber S, Feagan BG, Peyrin-Biroulet L, Vermeire S, Faes M, Harris K et al (2023) Filgotinib improved health-related quality of life and led to comprehensive disease control in individuals with ulcerative colitis: data from the selection trial. J Crohns Colitis 17:863–875. https://doi.org/10.1093/ecco-jcc/jjad018
16. Mazieres J, Kowalski D, Luft A, Vicente D, Tafreshi A, Gümüş M et al (2020) Health-related quality of life with carboplatin-paclitaxel or nab-paclitaxel with or without pembrolizumab in patients with metastatic squamous non–small-cell lung cancer. JCO 38:271–280. https://doi.org/10.1200/JCO.19.01348
17. Curigliano G, Dunton K, Rosenlund M, Janek M, Cathcart J, Liu Y et al (2023) Patient-reported outcomes and hospitalization data in patients with HER2-positive metastatic breast cancer receiving trastuzumab deruxtecan or trastuzumab emtansine in the phase III DESTINY-Breast03 study. Ann Oncol 34:569–577. https://doi.org/10.1016/j.annonc.2023.04.516
18. Weisel K, Dimopoulos MA, San-Miguel J, Paner A, Engelhardt M, Taylor F et al (2023) Impact of elotuzumab plus pomalidomide/dexamethasone on health-related quality of life for patients with relapsed/refractory multiple myeloma: final data from the phase 2 ELOQUENT-3 trial. HemaSphere 7:e843. https://doi.org/10.1097/HS9.0000000000000843
19. Loibl S, Loirat D, Tolaney SM, Punie K, Oliveira M, Rugo HS et al (2023) Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. Eur J Cancer 178:23–33. https://doi.org/10.1016/j.ejca.2022.10.003
20. Villacampa G, Falato C, Paré L, Hernando C, Arumí M, Saura C et al (2022) Pre-operative ribociclib plus letrozole versus chemotherapy: health-related quality of life outcomes from the SOLTI CORALLEEN trial. Eur J Cancer 174:232–242. https://doi.org/10.1016/j.ejca.2022.07.028
21. Fizazi K, Herrmann K, Krause BJ, Rahbar K, Chi KN, Morris MJ et al (2023) Health-related quality of life and pain outcomes with [(177)Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 24:597–610. https://doi.org/10.1016/S1470-2045(23)00158-4
22. Giuliano AE (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305:569. https://doi.org/10.1001/jama.2011.90
23. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL et al (2016) American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline: ACS/ASCO breast cancer survivorship guideline. CA: A Cancer Journal for Clinicians 66:43–73. https://doi.org/10.3322/caac.21319
24. Vaz-Luis I, Masiero M, Cavaletti G, Cervantes A, Chlebowski RT, Curigliano G et al (2022) ESMO Expert Consensus Statements on Cancer Survivorship: promoting high-quality survivorship care and research in Europe. Ann Oncol 33:1119–1133. https://doi.org/10.1016/j.annonc.2022.07.1941

25. European Organization for Research and Treatment of Cancer Quality of Life-Core30 (version 3). Available at: https://qol.eortc.org/questionnaires/
26. European Organization for Research and Treatment of Cancer Quality of Life-Breast23. Available at: https://qol.eortc.org/questionnaires/
27. European Organization for Research and Treatment of Cancer Quality of Life-Core30 Scoring Manual. Available at: https://qol.eortc.org/questionnaires/
28. European Organization for Research and Treatment of Cancer Quality of Life-Breast23 Scoring Manual. Available at: https://qol.eortc.org/questionnaires/
29. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MAA, Scott NW et al (2016) Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol 69:79–88. https://doi.org/10.1016/j.jclinepi.2015.08.007
30. Bloom JR (2002) Surviving and thriving? Psychooncology 11:89–92. https://doi.org/10.1002/pon.606
31. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. JCO 16:139–144. https://doi.org/10.1200/JCO.1998.16.1.139
32. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM (2011) Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. JCO 29:89–96. https://doi.org/10.1200/JCO.2010.28.0107
33. Mouelhi Y, Jouve E, Castelli C, Gentile S (2020) How is the minimal clinically important difference established in health-related quality of life instruments? Review of anchors and methods. Health Qual Life Outcomes 18:136. https://doi.org/10.1186/s12955-020-01344-w
34. Di Maio M, Basch E, Bryce J, Perrone F (2016) Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nat Rev Clin Oncol 13:319–325. https://doi.org/10.1038/nrclinonc.2015.222
35. Basch E (2010) The missing voice of patients in drug-safety reporting. N Engl J Med 362:865–869. https://doi.org/10.1056/NEJMp0911494
36. Yang LY, Manhas DS, Howard AF, Olson RA (2018) Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. Support Care Cancer 26:41–60. https://doi.org/10.1007/s00520-017-3865-7
37. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P et al (2016) Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. JCO 34:557–565. https://doi.org/10.1200/JCO.2015.63.0830
38. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C et al (2017) Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 318:197. https://doi.org/10.1001/jama.2017.7156
39. Barbera L, Sutradhar R, Seow H, Earle CC, Howell D, Mittmann N et al (2020) Impact of standardized Edmonton Symptom Assessment System use on emergency department visits and hospitalization: results of a population-based retrospective matched cohort analysis. JCO Oncol Pract 16:e958–e965. https://doi.org/10.1200/JOP.19.00660
40. Barbera L, Sutradhar R, Seow H, Mittmann N, Howell D, Earle CC et al (2020) The impact of routine Edmonton Symptom Assessment System (ESAS) use on overall survival in cancer patients: results of a population-based retrospective matched cohort analysis. Cancer Med 9:7107–7115. https://doi.org/10.1002/cam4.3374
41. Dong H, Kong X, Wang X, Liu Q, Fang Y, Wang J (2023) The causal effect of dietary composition on the risk of breast cancer: a Mendelian randomization study. Nutrients 15. https://doi.org/10.3390/nu15112586
42. Huang Y, Zhu T, Zhang X, Li W, Zheng X, Cheng M et al (2023) Longitudinal MRI-based fusion novel model predicts pathological complete response in breast cancer treated with neoadjuvant chemotherapy: a multicenter, retrospective study. eClinicalMedicine 58:101899. https://doi.org/10.1016/j.eclinm.2023.101899
43. Hall E, Cameron D, Waters R, Barrett-Lee P, Ellis P, Russell S et al (2014) Comparison of patient reported quality of life and impact of treatment side effects experienced with a taxane-containing regimen and standard anthracycline based chemotherapy for early breast cancer: 6year results from the UK TACT trial (CRUK/01/001). Eur J Cancer 50:2375–2389. https://doi.org/10.1016/j.ejca.2014.06.007
44. Husson O, De Rooij BH, Kieffer J, Oerlemans S, Mols F, Aaronson NK et al (2020) The EORTC QLQ-C30 summary score as prognostic factor for survival of patients with cancer in the "real-world": results from the population-based PROFILES registry. Oncologist 25:e722–e732. https://doi.org/10.1634/theoncologist.2019-0348
45. Wolberg WH, Romsaas EP, Tanner MA, Malec JF (1989) Psychosexual adaptation to breast cancer surgery. Cancer 63:1645–1655. https://doi.org/10.1002/1097-0142(19890415)63:8%3c1645::AID-CNCR2820630835%3e3.0.CO;2-8
46. Vinokur AD, Threatt BA, Vinokur-Kaplan D, Satariano WA (1990) The process of recovery from breast cancer for younger and older patients. Changes during the first year. Cancer 65:1242–1254. https://doi.org/10.1002/1097-0142(19900301)65:5%3c1242::AID-CNCR2820650535%3e3.0.CO;2-1
47. Lindley C, Vasa S, Sawyer WT, Winer EP (1998) Quality of life and preferences for treatment following systemic adjuvant therapy for early-stage breast cancer. JCO 16:1380–1387. https://doi.org/10.1200/JCO.1998.16.4.1380
48. Ganz PA (2002) Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. CancerSpectrum Knowl Environ 94:39–49. https://doi.org/10.1093/jnci/94.1.39
49. Au H-J, Eiermann W, Robert NJ, Pieńkowski T, Crown J, Martin M et al (2013) Health-related quality of life with adjuvant docetaxel- and trastuzumab-based regimens in patients with node-positive and high-risk node-negative, HER2-positive early breast cancer: results from the BCIRG 006 study. Oncologist 18:812–818. https://doi.org/10.1634/theoncologist.2013-0091
50. Roydhouse JK, Mishra-Kalyani PS, Bhatnagar V, Gutman R, King-Kallimanis BL, Sridhara R et al (2021) Does knowledge of treatment assignment affect patient report of symptoms, function, and health status? An evaluation using multiple myeloma trials. Value Health 24:822–829. https://doi.org/10.1016/j.jval.2020.12.015