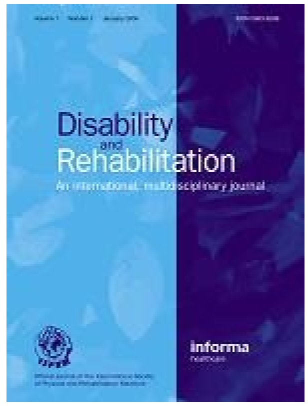

The minimal clinically important difference in the treadmill six-minute walk test in women with breast cancer during and after oncological treatments

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This study is entitled "The minimal clinically important difference in the treadmill six-minute walk test in women with breast cancer during and after oncological treatments".

This work aims to determine the minimal clinically important difference for treadmill 6-minute walk test in women with breast cancer, at two time points: during and after oncological treatments. It establishes cut-off points for this population which could be used for example to monitor the progress of patients in the survival stage; or monitor whether their health status worsens during treatments. If they can be monitored in a simple way, it is also easier to see changes in the physical condition or health of these women. Furthermore, with the treadmill, the 6-minute walk test can be performed under more control.

The minimal clinically important difference in the treadmill six-minute walk test in women with breast cancer during and after oncological treatments

Short title: MCID in the 6MWT in women with breast cancer

Word count: 2955

1. INTRODUCTION

Breast cancer and its treatment have important impacts on women's health, including physical and psychological alterations [1] and even loss of functional capacity [2]. Functional capacity is the ability to perform activities of daily living. Particularly important among them is the ability to walk since it facilitates self-sufficiency and provides information about the state of the cardiopulmonary [3] and musculoskeletal systems [4]. The 6-minute walk test (6MWT) – a submaximal walking test – is commonly used to determine functional exercise capacity in patients with different ailments, including cancer [4]. Indeed, it is often used in physical therapy in oncology patients since it is easily performed [5] and provides prognostic [6] and survival information [4], and key information is provided by the minimal clinically important difference (MCID) in the walked distance.

The MCID is the smallest change required to affect patient-perceived outcomes and, hence, reflects whether the change is relevant [7]. The MCID is valuable to patients with cancer, clinicians and researchers, and allows interpretation of any change in performance of the 6MWT. Identification of reference values that highlight changes in patients' health with cancer is essential to analyse trends in recovery and to provide adequate interventions. This will help to offer a continuum cancer care to prevent physical deterioration [8]. Anchor- and distribution-based methods are the most commonly used methods to calculate the MCID [9], and the combination of these approaches has been previously used successfully to determine the MCID in the 6MWT [9,10,19,11–18].

A review [20] established that the MCID of the 6MWT for the geriatric population is between 14 and 30.5 metres, and 44 metres has been considered meaningful progress in people after stroke [21]. Considering certain cancer settings, Granger and collaborators [15] obtained the MCID in adults with lung cancer and identified an MCID ranging from 22 to 42 metres. Meanwhile, Shan and collaborators [22] worked with patients with multiple myeloma undergoing autologous haematopoietic cell transplantation (auto-HCT), although their efforts were inconclusive due to the lack of practicality of the 6MWT. To our knowledge, the MCID of the 6MWT in breast cancer is not known in either active cancer patients or cancer survivors. Knowledge of the MCID for this group of patients would further support physical therapists involved in the oncology setting.

The international consensus [23] on the performance of the 6MWT advises the use of a 25- or 30-m hallway without obstacles or distractions for standardization and optimal conduction of the 6MWT. However, many physical therapy facilities have insufficient space to meet these requirements, which has led clinicians and researchers to investigate the use of alternative distances [24] and even treadmills as possible substitutes to the recommended hallway [25]. Despite helping to improve the feasibility of conducting the 6MWT in areas with limited space, the use of a treadmill for the 6MWT remains controversial. While some studies have shown that a treadmill is an adequate alternative to assess the distance walked (the primary endpoint of the test) [26] and the heart rate achieved during the 6MWT [27], other studies have found significant differences in the distance walked when the 6MWT is performed on a treadmill rather than overground [27–29]. In general, it appears that distances walked in the 6MWT on a treadmill are shorter than the distances achieved using the overground gold standard approach [28–30]. Several hypothesized reasons for this difference include lack of familiarization with the treadmill [28,31], a constant and limited speed [31], and different walking biomechanics compared to overground walking [32]. Based on the currently available evidence, normal reference data for the 6MWT completed on the ground versus the treadmill are not interchangeable.

Despite this, studies have used the treadmill for performing the 6MWT to check the health status of patients with chronic obstructive pulmonary disease [33] or pulmonary arterial hypertension [31], with few conducted specifically in cancer and even less in patients with breast cancer [34,35]. More studies are needed to standardize the development of the 6MWT on treadmills [28]. Therefore, this study aims to determine the MCID of the treadmill 6MWT in a sample of patients with breast cancer in two different situations: during anticancer treatment (during-chemotherapy group) and once these treatments have been completed (after-treatment group).

2. METHODS

2.1. Study design and sample

A secondary analysis was carried out with two data sets from two randomized controlled trials developed by the CUIDATE group (from the PAIDI BIO277 group) with 24 physical exercise sessions in accordance with the American College of Sport Medicine recommendations for patients with cancer [8]: e-CUIDATECHEMO (Clinicaltrials.gov

NCT02350582) [36] and eCUIDATE (Clinicaltrials.gov NCT01801527)[34], which were approved by the Research Ethics Committee of the University of Granada (FIS PI10/02749-02764 and PI-0457-2010, respectively) (**Figure 1**). The STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement was followed [37]. Participants were referred by their treating oncologist at the Virgen de las Nieves Hospital (Oncology and Breast Unit) from March 2012 to November 2013 (eCUIDATE) and from September 2013 to June 2015 (e-CUIDATECHEMO).

Patients were recruited if they i) were between 25 and 80 years old, ii) had a breast cancer diagnosis (I-IIIa), iii) were undergoing chemotherapy (e-CUIDATECHEMO) or had finished medical therapy (eCUIDATE), and iv) had no medical contraindications to participation. Patients were excluded if they had a chronic disease or orthopaedic issues that influenced their physical abilities.

2.2. Procedure and outcome measures

Participants recruited to both RCTs performed the 6MWT and completed the European Organization for Research and Treatment of Cancer questionnaire (EORTC-QLQ-C30) at baseline and again 8 weeks later. All assessments were completed in the physical therapy laboratory in the Health Science Faculty from Granada by the same blinded physiotherapist from the CUIDATE group, who had 4 years of experience in the evaluation of patients with cancer, according to the Helsinki Declaration (WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2017) and the Spanish Biomedical Research Law (Organic Law 14/2007, of 3rd July).

The 6MWT assessments were performed according to the European Respiratory Society/American Thoracic Society instructions [23], with the exception of being conducted on a treadmill instead of overground. The treadmill (H-P-COSMOS for graphics, Germany) test was performed using a previously published protocol [38] (**Supplementary material 1**). All participants received familiarization training on the treadmill and were asked to rest, sitting for more than 10 minutes, prior to testing. The Borg rating of Perceived Exertion (RPE), peripheral capillary oxygen saturation (SpO_2) and heart rate were collected before and after the test as control variables. Participants were instructed to walk as fast as possible for 6 minutes with no treadmill inclination and an initial speed of 0. Participants were able to see only the speed, which they were able to increase or decrease by themselves. The test was performed twice by each participant with an active rest period of 15 minutes. The greatest 6MWT distance in metres was included in the analysis. This test has shown good reliability, with an intraclass correlation coefficient (ICC) of 0.78 for distance.

The physical function (PF) domain of the EORTC-QLQ-C30 Spanish version 3.0 was used as an anchor to calculate the MCID. This questionnaire includes both single- and multi-item scales (functional, symptoms and six single items) that are rated from 1 (not at all) to 4 (very much) and are transformed into a score of 0 to 100. A change > 5 points in PF is considered a minimal relevant threshold [39] and was used to classify participants into subgroups that achieved a 'positive change' ($\geq$5 points) or remained 'unchanged' ($<$5 points) between time points [16]. The PF domain has a test-retest reliability of $r=0.91$ [40].

The demographic and clinical characteristics of participants were collected with a self-report questionnaire, a plastic tape measure and bioelectrical impedance analysis (InBody 720; Biospace, Gateshead, UK).

2.3. Statistical analysis

Analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistic for Windows, Armonk, NY, USA version 24.0). Only participants with repeated 6MWT and PF domain results were considered for analysis. The normality of the distribution of the variables was checked with the Shapiro-Wilk test. The demographic and clinical characteristics are expressed as the mean (m) and standard deviation (SD) for continuous variables and as a number (n) and percentage (%) for categorical variables. Based on the PF domain results, participants were divided into a 'positive change' subgroup (≥5 points difference in the PF domain between baseline and follow-up) and an 'unchanged' subgroup (<5 points difference in the PF domain between baseline and follow-up) [15]. The differences between groups in demographic and clinical characteristics were calculated using *t* tests for independent samples (continuous variables) and X^2 analysis (categorical variables). The change in 6MWT distance and PF domain between two time points was calculated using repeated-measures ANOVA. The test retest reliability was calculated with an intraclass correlation coefficient (ICC).

The anchor-based method contrasts the change in a patient-reported outcome with another measure of change [41]. To determine whether the change in the 6MWT established a difference between the 'positive change' and 'unchanged' subgroups (with the PF domain of EORTC-QLQ-C30 as the anchor), we calculated the sensitivity and specificity for each cut-off point. The optimal cut-off point was obtained with the Youden Index [42].

Distribution-based methods were used to determine the MCID based on statistical characteristics of the patient-reported outcomes with different methods, such as the standard error of measurement (SEM) and effect size (ES) [41], using the following formulas: $SEM=\sigma_1 \sqrt{(1- r)}$, where σ_1= standard deviation (SD) at baseline r= test-retest reliability coefficient and ES=0.5 X SD of the change in distance in the 6MWT [15].

3. RESULTS

3.1. Demographic and clinical characteristics

One hundred and twelve patients with breast cancer were included in this study. The average age of the participants were mean (SD) 49.29±8.40 years (range 30-72) for patients in the 'during-chemotherapy' group and 48.85±8.53 years (27-70) for patients in the 'after-treatment' group. Additional participant demographic and clinical characteristics are shown in **Table 1**. From baseline to 8 weeks, 21.1% of participants (n=8) were classified in the 'positive change' subgroup based on the EORTC-QLQ-C30 PF domain, whereas 78.9% (n=30) were classified in the 'unchanged' subgroup for patients during chemotherapy. Overall, 51.4% of participants (n=38) were classified as exhibiting a 'positive change', whereas 48.6% (n=36) were classified as 'unchanged' for patients in the after-treatment group. There were no significant differences between the levels of moderate and vigorous physical activity between the groups within the time periods (**Table 1**).

3.2. Changes in the 6MWT distance and the PF domain between the two time points

In the during-chemotherapy group, in the 'positive change' subgroup, the mean difference in the 6MWT walked distance between the baseline and the 8-week follow-up was +100.1 (90.2) m; in the 'unchanged' subgroup, the mean difference between timepoints was -

7.00 (86.9) m, with p=0.004; F=0.004. In the after-treatment group, in the 'positive change' subgroup, the mean difference in the 6MWT walked distance between the baseline and the 8-week follow-up was +85.1 (83.0) m, and in the 'unchanged' subgroup, the mean difference between time points was +46.8 (75.1) m, with p=0.043; F=0.292 (**Figure 2A and 2B**).

3.3. Test rest reliability of the 6MWT distance from test to retest

The test-retest reliability of the 6MWT distance was moderate in the during-chemotherapy group, with an ICC= 0.746 (95.0% CI: 0.51-0.86), and excellent in the after-treatment group, with an ICC= 0.934 (95.0% CI: 0.89-0.95).

3.4. MCID calculation – anchor-based approach

The areas under the receiver operating characteristic (AUROC) curves were .808 (p=.008, 95.0% CI 0.63-0.98; **Figure 3A**) in the during-chemotherapy group and .646 (p=.032, 95.0% CI .52-.77; **Figure 3B**) in the after-treatment group. The optimal cut-off points for clinically relevant decline were -58.9 m (with a sensitivity of 87% and a specificity of 70%) and -42.7 m (with a sensitivity of 97% and a specificity of 91%), respectively.

3.5. MCID calculation – distribution-based approach

The distribution-based methods calculated for the during-chemotherapy and after-treatment groups showed MCID estimates of 66.5 m and 41.4 m based on SEM and of 41.5 m and 40.5 m based on ES, respectively.

4. DISCUSSION

The results of this study have important clinical applications, as we have established a minimum distance for the 6MWT using a treadmill. We determined cut-off points in order to have reference values in women with breast cancer during and after medical treatments, expanding the possibilities of the use of the 6MWT to improve the monitoring and evaluation of physical health status. Our sample of middle-aged women with breast cancer was representative of this population, and the reliability of the 6MWT distance was moderate and excellent in the during-chemotherapy and in the after-treatment group respectively. We have estimated that changes between 41 and 66 m for women in the during-chemotherapy group and between 40 and 42 m for women in the after-treatment group in the 6MWT distance on a treadmill indicates a significant clinical improvement. Women with breast cancer may experience adverse side effects associated with cancer diagnosis and treatments, which can lead to significant physical function deterioration [43] that has been related not only to a decrease in health status [44] but also to increased risks of recurrence and mortality [45]. For these reasons, researchers must have valid reference values to identify changes in patients' health [46].

The range of MCID for the 6MWT in chronic diseases has been established as 14 to 30.5 m [20]. However, previous evidence in different populations suggests that it is possible to find higher values, up to 58.5 m, in patients with idiopathic pulmonary fibrosis [11,14] and even 167 m in women with fibromyalgia [47]. The values we report may provide an indication of the MCID for the 6MWT in patients with cancer; however, it is clear that the MCID must be set for each specific condition [48]. Previous studies conducted in lung cancer [15,20] showed MCID ranges of 14 to 42 m in studies using an overground 6MWT. The wide range of MCIDs may be explained by factors such as methodologies to calculate the MCID score, anchors used, levels of physical fitness, demographic characteristics, or the instrument used [48]. Although the previous results could be an approximate reference, more specific values are required for the use of the treadmill in the 6MWT for patients with breast cancer.

The American Thoracic Society (ATS) does not recommend the use of a treadmill when conducting the 6MWT [25]; however, this advice was based on the result of only one study [30]. Subsequent evidence is not in agreement concerning the reliability of the 6MWT on a treadmill compared to overground [28]. Despite the ATS guidelines, the 6MWT on a treadmill has been used in subsequent trials [27–30] to assess functional exercise capacity and to compare with reference values for the 6MWT overground. More evidence on the reliability of reference values for the 6MWT on a treadmill is required across different clinical populations.

According to previous studies [11,12,14,15], our results report a wide MCID range in the during-chemotherapy group, although the values were very similar to the references established for the 6MWT in a corridor. This large difference in values could be due to the impact on physical function while these women are receiving treatment [49] and may be due to the use of both anchor- and distribution-based methods. The two methods were frequently used together in previous studies to calculate the MCID for the 6MWT [9–14,16–19]; additionally, we used an increase ≥5 points in the PF domain of the EORTC-QLQ-C30, which has been widely accepted for its ability to determine physical improvement [50]. This method considers the importance of the change but is sensitive to the degree of variability in the sample, which was large in this group. With our results, it may be adequate to think that MCIDs of approximately 54 m in the during-chemotherapy group and 41.5 m in the after-treatment group are appropriate minimum improvement points for monitoring physical health.

The MCID helps both clinicians and researchers interpret changes in health status objectively, but our study also enables the detection of physical deterioration, a risk factor for poor health, recurrence, and mortality in patients with cancer [51]; thus, it has important clinical and research implications. In addition, identifying patients with physical deterioration and providing them with supportive programs may be useful for determining sample sizes in research studies, establishing new research designs, selecting variables or assessing the effectiveness of new approaches. Additionally, it is important to note that obtaining a reference value, such as the MCID, is necessary for a continuously growing clinical population, such as women with breast cancer. In a clinical context, the use of a treadmill provides a logistical advantage since it is often difficult to find a hallway that is free of distractions.

4.1. Limitations

This study has several limitations. One of these is the use of a treadmill for the 6MWT. We know that the main limitation is the inadequacy of the comparison with the values of previous studies conducted in corridors, but we believe that the treadmill is a widely used resource in clinical situations. In addition, the participants of the studies analysed were part of clinical trials with different interventions, although there were no differences between the groups in terms of the level of moderate and intense physical activity that they performed, as measured with accelerometery. More studies are needed to confirm these results in women with breast cancer.

In conclusion, our study showed the MCID of the 6MWT distance, when conducted on a treadmill, in women with breast cancer is between 41 and 66 m in patients undergoing active treatment and between 41 and 43m in patients after completion of treatment. These values could be used by clinicians and researchers as reference data to interpret changes in the physical health status of their patients with breast cancer when using the 6MWT.

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Conflict of interest

The authors declare no conflict of interests

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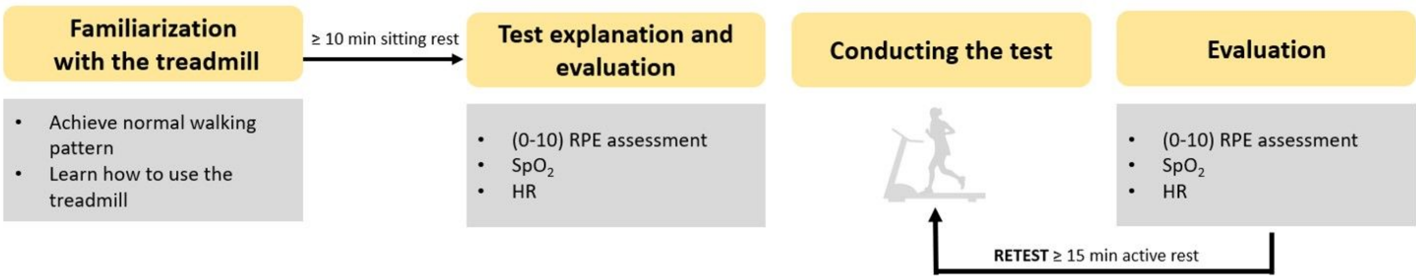
Appendix

Appendix 1: 6MWT on treadmill assessment protocol

Abbreviations: 6MWT: 6-minute walk test, HR: heart rate, SpO_2: peripheral capillary oxygen saturation, RPE: rating of perceived exertion



Tables

Table 1: Demographic and clinical characteristics of the groups.

	Time periods					
	During-chemotherapy		p	After-treatment		p
Characteristic	Positive change group (n= 8)	Unchanged group (n= 30)		Positive change group (n= 38)	Unchanged group (n= 36)	
		Sociodemographic characteristics				
Age (year), mean±SD	47.75±6.60	49.70±8.78	.563	47.03±9.02	50.78±8.00	.063
Education n (%)			.099			.647
Basis	4 (50)	12 (40)		15 (39.5)	17 (47.2)	
Medium	0 (0)	11 (36)		11 (28.9)	11 (30.6)	
Superior	4 (50)	7 (23.3)		12 (31.6)	8 (22.2)	
Occupation, n (%)			.905			.446
Home duties	2 (25)	7 (23.3)		13 (34.2)	16 (44.4)	
Full time	2 (25)	5 (16.7)		5 (13.2)	6 (16.7)	
Temporary sick leave	0 (0)	1 (3.3)		12 (31.6)	11 (30.6)	
Permanent sick leave	4 (50)	17 (56.7)		8 (21.1)	3 (8.3)	
Smoking status n (%)			.663			.840
Never smoker						
Current smoker	4 (50)	11 (36.7)		20 (52.6)	19 (52.8)	
Ex-smoker	1 (12.5)	8 (26.7)		7 (18.4)	5 (13.9)	
	3 (37.5)	11 (36.7)		11 (28.9)	12 (33.3)	
Alcohol intake, n (%)			.863			.414
Never						
Monthly	4 (50)	12 (40)		19 (50)	15 (41.7)	
Weekly	2 (25)	7 (23.3)		6 (15.8)	7 (19.4)	
Daily	2 (25)	9 (30)		11 (28.9)	14 (38.9)	
	0 (0)	2 (6.7)		2 (5.3)	0 (0)	
		Clinical characteristics				
Cancer stage, n (%)			.141			.108
I	3 (37.5)	8 (26.7)		17 (44.7)	8 (22.2)	
II	1 (12.5)	15 (50)		16 (42.1)	23 (63.9)	
III	4 (50)	7 (23.3)		5 (13.2)	5 (13.9)	
Medical treatment, n (%)			.421			.998
No treatment	2 (25)	4 (13.3)		0 (0)	0 (0)	
Radiotherapy	0 (0)	0 (0)		1 (2.6)	1 (2.8)	
Chemotherapy	6 (75)	26 (86.7)		2 (5.3)	2 (5.6)	
Radiotherapy & chemotherapy	0 (0)	0 (0)		35 (92.1)	33 (91.7)	
Menopause, n (%)	5 (62.5)	17 (56.7)	.767			.264
No	3 (37.5)	13 (43.3)		5 (13.2)	2 (5.6)	
Yes				33 (86.8)	34 (94.4)	
Accelerometry (MVPA) , mean±SD	84.92±33.04	84.41±38.81	.974	77.41±27.18	74.97±34.04	.734
Body Mass Index, mean±SD	24.65±4.69	27.46±4.26	.113	26.11±5.72	28.30±5.80	.105

P values of between-group differences using *t*-test for independent samples (continuous variables) and X^2 analysis (categorical variables). n = sample size. SD: standard deviation. MVPA: moderate-vigorous physical activity $^*P<0.05$.

FIGURE LEGENDS

Fig.1 Patients flow in both studies

Fig. 2A Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the after-treatment group.

Fig. 2B Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the during-treatment group.

Fig.3A The Area Under Receiver Operating Characteristic (AUROC) curve in the during-treatment group

Fig.3B The Area Under Receiver Operating Characteristic (AUROC) curve in the after-treatment group

Figure 1: Patients flow in both studies

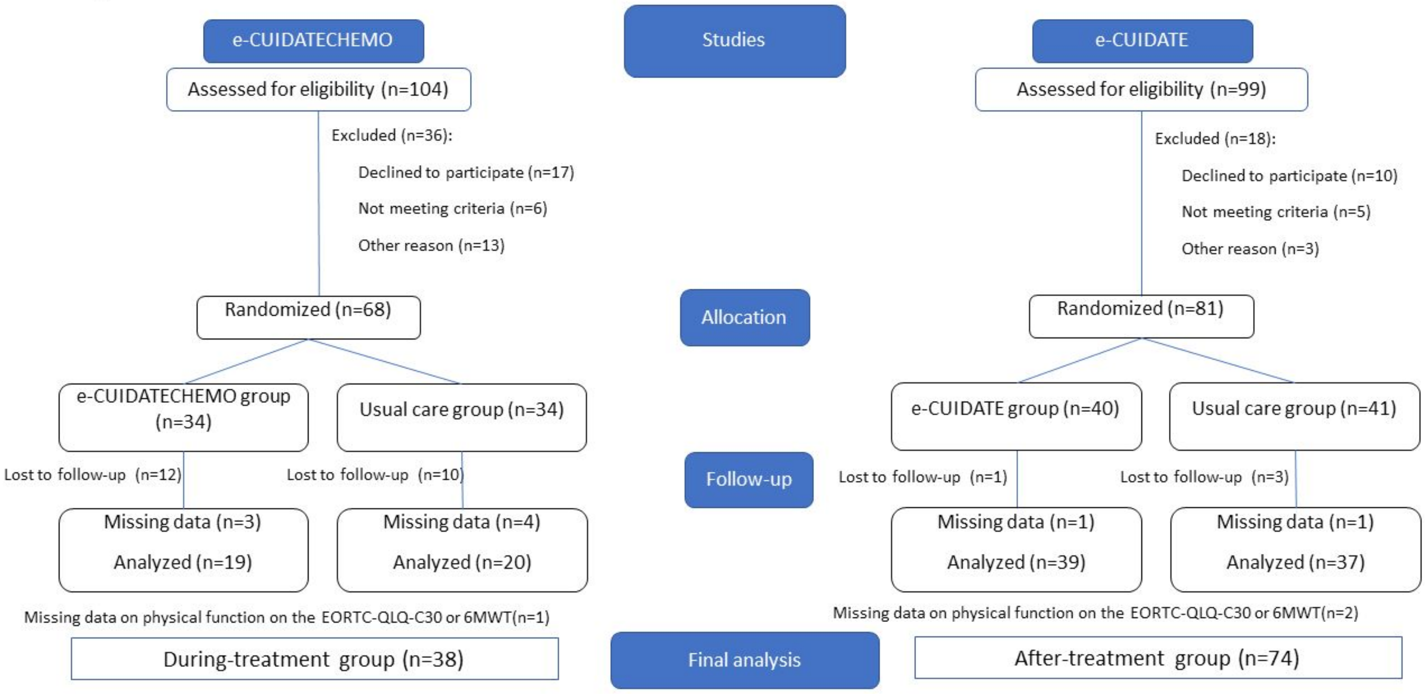


Fig.2A Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the during-chemotherapy group.

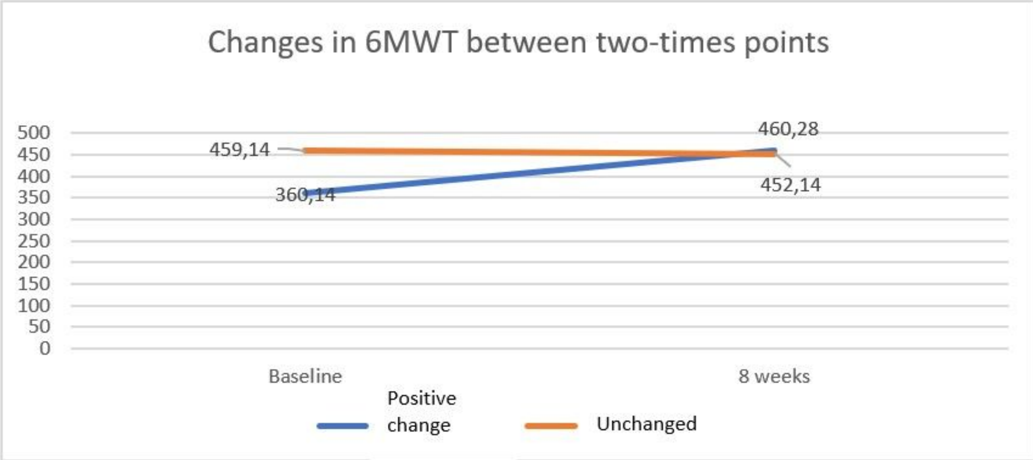


Fig.2B Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the after-treatment group.

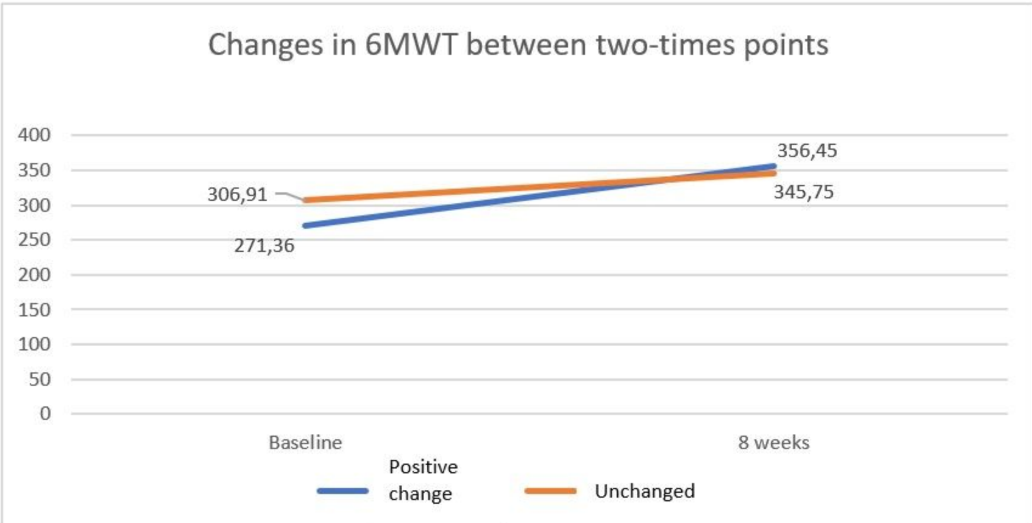


Fig.3A The Area Under Receiver Operating Characteristic (AUROC) curve

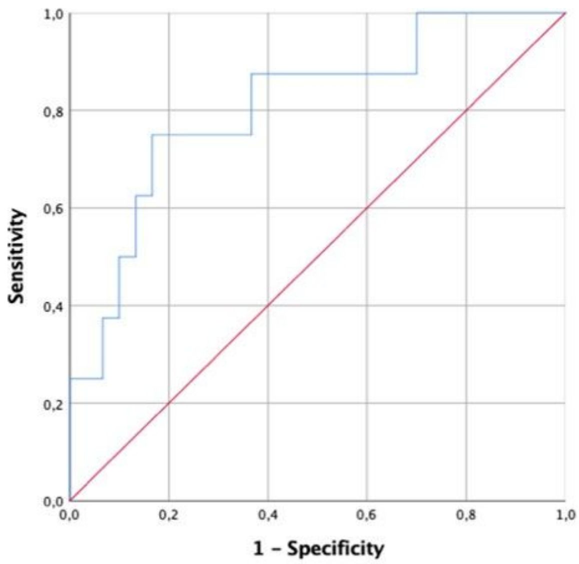
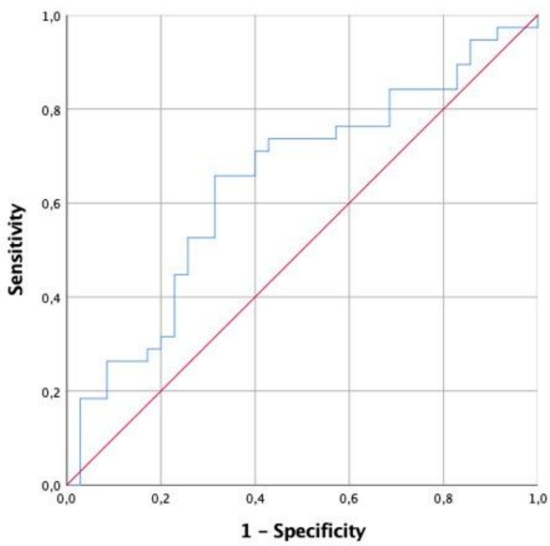


Fig. 3B The Area Under Receiver Operating Characteristic (AUROC) curve



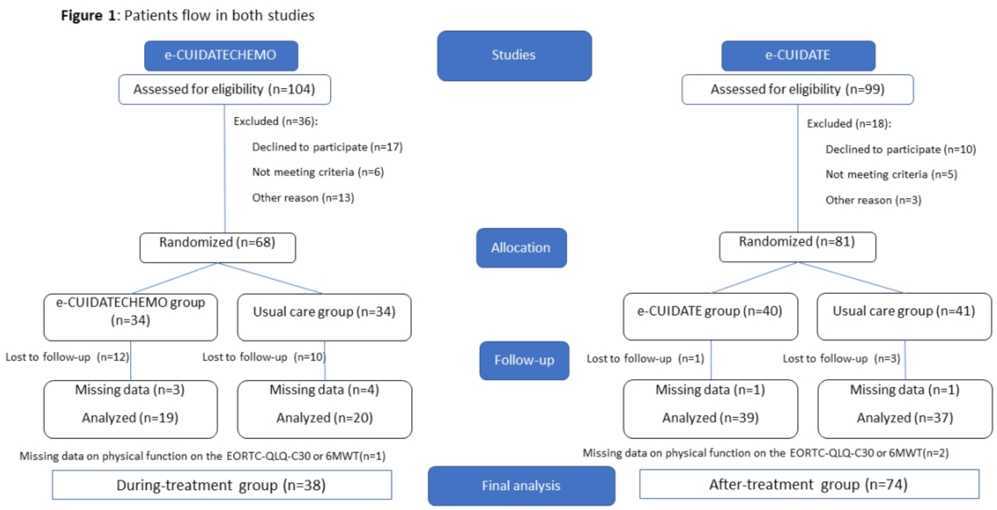


Fig.1 Patients flow in both studies

855x481mm (38 x 38 DPI)

Fig.2A Change in the 6MWT distance (m) between baseline and 8 weeks tests in the ‘positive change’ and the ‘unchanged’ subgroups from the during-chemotherapy group.

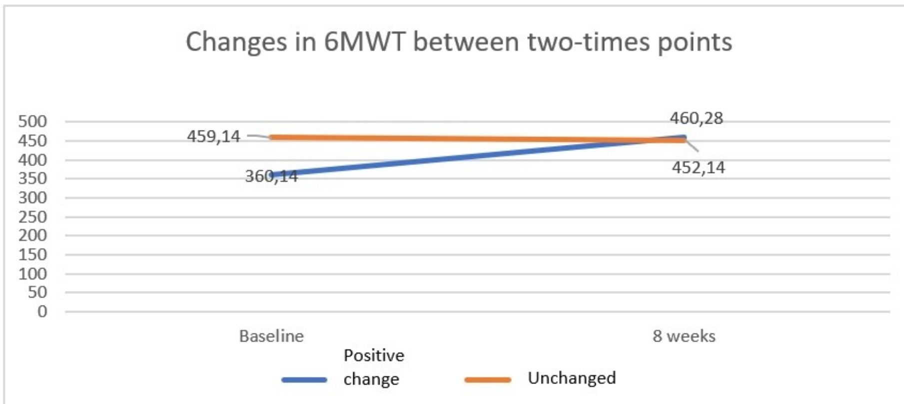


Fig. 2A Change in the 6MWT distance (m) between baseline and 8 weeks tests in the ‘positive change’ and the ‘unchanged’ subgroups from the after-treatment group.

197x113mm (120 x 120 DPI)

Fig.2B Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the after-treatment group.

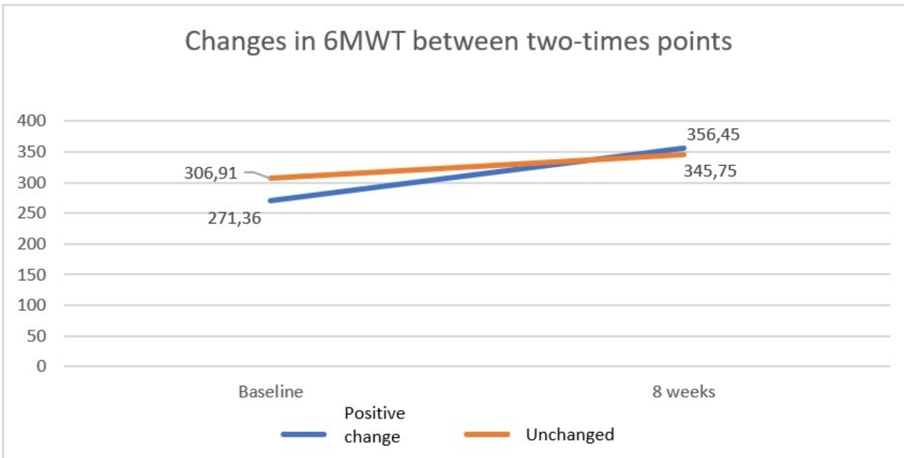


Fig. 2B Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the during-treatment group.

197x132mm (120 x 120 DPI)

Fig.3A The Area Under Receiver Operating Characteristic (AUROC) curve

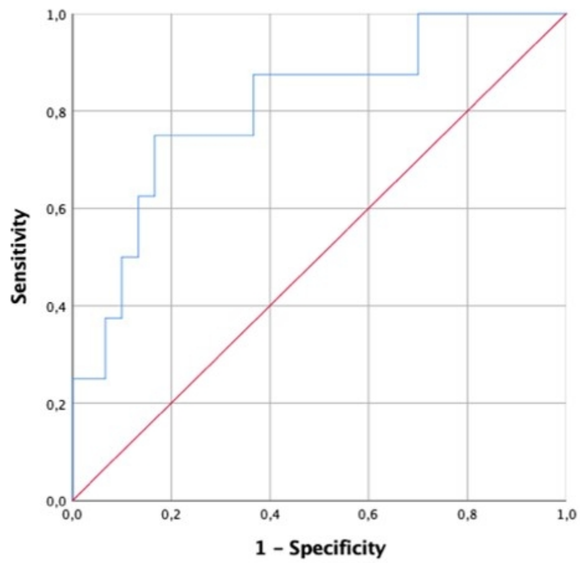


Fig.3A The Area Under Receiver Operating Characteristic (AUROC) curve in the during-treatment group

170x133mm (120 x 120 DPI)

Fig. 3B The Area Under Receiver Operating Characteristic (AUROC) curve

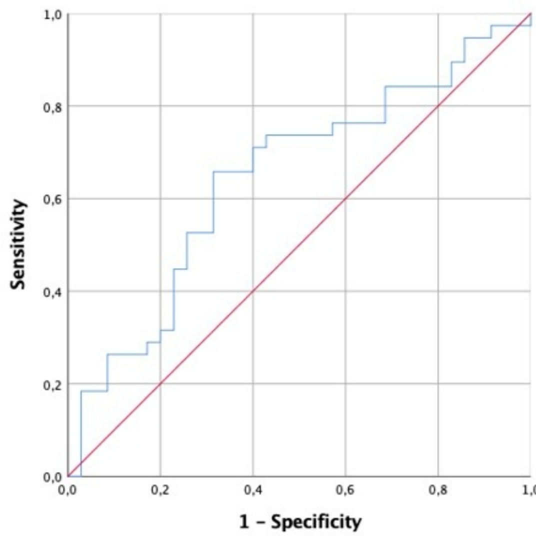


Fig.3B The Area Under Receiver Operating Characteristic (AUROC) curve in the after-treatment group

172x138mm (120 x 120 DPI)