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RESEARCH ARTICLE

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Tracking cancer-related fatigue during chemotherapy: Insights from a comparative cohort study of early breast cancer patients

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Abstract

Cancer-related fatigue (CRF) is a multifactorial symptom commonly experienced by breast cancer patients treated with chemotherapy (CT) that impairs quality of life and may influence cancer recurrence by reducing treatment compliance. This cohort study examined the kinetics of CRF throughout CT in breast cancer patients and determined its relationship with exercise-related variables. One hundred breast cancer patients were included. Three time points were investigated: pre-CT, 8 weeks, and post-CT. Patients were categorized as fatigued or non-fatigued according to their FACIT-F score. Exercise capacity (assessed using the 6-minute walking test), muscle mass and force, neuromuscular fatigue, and physical activity level were measured. Among the seven patterns of CRF trajectories identified, three represented 78% of the fatigued patients. Fatigued patients exhibited reduced exercise capacity compared to non-fatigued patients during CT ($p = 0.001$). This was associated with greater knee extensor ($p < 0.001$) and handgrip ($p = 0.009$) neuromuscular fatigue and lower physical activity level ($p < 0.001$) in fatigued patients. The model combining knee extensors neuromuscular fatigue ($p = 0.007$) and force ($p = 0.081$), 6-minute walking test distance ($p < 0.001$) and physical activity level ($p = 0.029$) explained 39% of the variance in the FACIT-F score evolution from pre- to post-CT. The dissociation between fatigued versus non-fatigued patients highlighted that CRF was associated with altered exercise capacity and neuromuscular fatigue. Exercise-related variables seem to play an important role in CRF evolution during CT, suggesting that exercise training should be initiated at the start of CT.

KEYWORDS
exercise capacity, muscle force, muscle mass, neuromuscular fatigue, six-minute walk test

Abbreviations: 6-MWT, 6-minute walking test; CRF, cancer-related fatigue; CT, chemotherapy; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GPAQ, Global Physical Activity Questionnaire; ICANS, Institut de Cancérologie Strasbourg Europe; MET, metabolic equivalents; ROC, Receiver Operating Characteristic.

Joris Mallard and Elyse Hucteau have contributed equally to this study.

What's New?

Cancer-related fatigue is a multifactorial symptom commonly experienced by breast cancer patients treated with chemotherapy. Here, the authors investigated the temporal associations between cancer-related fatigue and exercise capacity to better tailor exercise interventions during chemotherapy. The cohort study identified seven cancer-related fatigue trajectories, with three of them experienced by 78% of patients. Cancer-related fatigue was associated with reduced exercise capacity, neuromuscular fatigue, and lower physical activity level. One model based on four exercise-related parameters explained 39% of the variance in cancer-related fatigue evolution, emphasizing the need for early exercise interventions prioritizing both exercise capacity and neuromuscular force.

1 | INTRODUCTION

Cancer-related fatigue (CRF) is a multifactorial symptom[1–3] commonly experienced by breast cancer patients treated with chemotherapy (CT).[4] Clinically, CRF is defined as a persistent, subjective sense of tiredness related to cancer or treatment that interferes with usual functioning and is not fully reversed by rest.[4–6] Importantly, CRF leads to impairments in patients' quality of life[7,8] and may influence cancer recurrence by reducing treatment compliance.[9,10] This context explains why understanding the development of CRF is of particular interest in oncology.

CRF is subjective in nature, and its development is likely individual.[4,5] For example, CRF trajectories were reported from pretreatment to 18 months posttreatment in 270 patients with breast cancer.[11] However, this study documented the evolution of CRF at multiple time points after treatment completion but not during treatment. While CRF can persist in cancer survivors,[12–14] CT treatment has been identified as a major risk factor.[15] Recently, our group investigated CRF prevalence during CT in breast cancer patients and reported that CRF development occurred mainly within the first 8 weeks of CT, without further change until the end of treatment.[16] Since CRF is an early symptom experienced by patients with breast cancer,[17] its development during CT treatment should be investigated by identifying any specific patterns and early causes/consequences for a better understanding and management of the disease.

CRF can be explained by numerous factors of biological, demographic, psychosocial, behavioral, and physiological origins.[3,18] In this context, factors related to exercise capacity are of particular interest for developing non-pharmacological preventive strategies,[19,20] such as exercise training that is considered the most efficient strategy for reducing CRF.[21] More precisely, aerobic capacity and neuromuscular function, two physiological factors that can be improved by specific exercise training programs,[22] are reduced in fatigued compared to non-fatigued cancer patients.[19,20] Moreover, one to two-thirds of the variance in CRF is explained by neuromuscular deconditioning, characterized by reduced muscle force,[23–25] increased exercise-induced neuromuscular fatigue[23–25] and reduced muscle mass.[26] However, while these investigations provide insightful evidence about the physical causes and consequences of CRF, it is important to note that these studies were cross-sectional in design and included only cancer survivors from multiple cancer sites. Therefore, investigating the temporal associations between CRF and exercise capacity is needed to improve tailored exercise training interventions[25] during breast cancer CT treatment, when CRF increases, rather than after treatment completion, when CRF usually plateaus.[12,13]

In this context, the present cohort study aimed to examine the kinetics of CRF throughout CT treatment in breast cancer patients to identify potential specific patterns in its trajectories. Additionally, we also investigated the correlation between CRF, neuromuscular fatigue, and exercise capacity.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Breast cancer patients included were asked to participate at three time points: before the first CT administration (pre-CT), 8 weeks later, and within 2 weeks after CT completion (post-CT).

The data from this study constitute a further analysis of a previous study that investigated the development of skeletal muscle deconditioning during CT treatment in breast cancer patients.[16] We therefore allocated patients from this cohort study in the clinically fatigued or non-fatigued group a posteriori to provide new insights.

2.2 | Measurements

2.2.1 | Cancer-related fatigue

Cancer-related fatigue was measured via the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) subscale, as recommended for this population.[27]

2.2.2 | Exercise capacity

The 6-minute walking test (6-MWT) was used as a reflection of overall submaximal exercise capacity.[28] Patients walked alone with no disturbance in a covered, flat, straight, well-delineated, 20 m corridor. Patients were asked to cover the greatest possible distance, and the total distance walked during the test (in meters) was used to assess exercise capacity.

2.2.3 | Muscle mass

Whole skeletal muscle mass was determined via a bioelectrical impedance analysis device (SECA mBCA 515, SECA, Hamburg, Germany).[29] Each visit was performed at the same time of day, with the patient in underwear and refraining from water consumption 1 h prior.

2.2.4 | Muscle force

Knee extensors muscle force was assessed in a seated position with the hip and knee joints fixed at 100° and 90°, respectively (where 180° represents full extension), and aligned with the frontal axis. The lower right leg was strapped above the ankle to an ergometer connected to a force transducer (Force sensor kit, Chronojump, Barcelona, Spain). The handgrip muscle force was measured via a handgrip dynamometer (Takeï, TK200; Takei Scientific Instruments, Tokyo, Japan). Patients sat upright in a chair with their feet touching the ground. The dominant arm was placed with the elbow flexed at 90° on a table, and the forearm and hand were placed in a neutral position. For each muscle group, after familiarization and a standardized warm-up, patients were asked to perform three 3-s maximal voluntary isometric contractions under verbal encouragement. There was a 30-s rest period between each contraction.[30] The mean force value of the three trials was subsequently calculated at each time point and reported in Newtons (N).

2.2.5 | Neuromuscular fatigue

For both knee extensors and handgrip muscles, the development of neuromuscular fatigue was assessed during 10 3-s maximal voluntary isometric contractions under verbal encouragement with a 2-s rest period between each contraction. Neuromuscular fatigue was calculated as the percent difference in peak force between the first contraction and the last contraction.[31]

2.2.6 | Physical activity level

Physical activity level was assessed via the 16-item Global Physical Activity Questionnaire (GPAQ) version 2.[32] A global score was calculated in metabolic equivalents (MET-min/week), in which a higher score was associated with a better physical activity level.

2.3 | Sample size and statistical analysis

This further analysis was performed on the 100 patients with breast cancer included in the original publication.[16] In this study, patients were allocated a posteriori in the fatigued or non-fatigued patient group according to their FACIT-F score.[27] More precisely, patients were classified as clinically fatigued if their FACIT-F score was ≤34 and non-fatigued if their score was >34.[33] This score was determined at pre-CT, 8 weeks, and post-CT, and patients were therefore (re)allocated to the fatigued or non-fatigued patient group at each time point. This approach was used to determine the different patterns of CRF.

The normality of the data was tested through Shapiro–Wilk tests, and the data were found to be normally distributed for each variable. The homogeneity of variances was then confirmed with the Levene test. Two-way mixed-design ANOVAs with repeated measures were used (group [fatigued vs. non-fatigued] × time [pre-CT, 8 weeks, post-CT]) to compare the influence of CRF on each exercise-related variable. Two-way ANOVAs with repeated measures (pattern [different patterns] × time [pre-CT, 8 weeks, post-CT]) were used to compare each exercise-related variable between the patterns of CRF. For this analysis, only the patients who performed measurements at the three time points were included. Two-way mixed ANOVAs with repeated measures were used (group [fatigued vs. non-fatigued] × time [pre-CT to 8 weeks, 8 weeks to post-CT, pre- to post-CT]) to compare the influence of CRF on the evolution of exercise-related variables. When a difference was found, a Receiver Operating Characteristic (ROC) curve was generated to determine the cutoff value. For all ANOVAs, a Greenhouse–Geisser correction was used when sphericity was violated. When a significant interaction effect was found, multiple comparison analysis was performed via the Sidak post hoc test. Simple linear regressions were calculated to determine correlations between CRF and the exercise-related variables (using their performance at a given time and their evolution during treatment). Multiple regressions were performed when several significant correlations were found. Statistical significance was set at $p \le 0.05$. Statistical analyses were performed, and graphs were generated with GraphPad Prism 10 software, and all values are expressed as the means ± SDs.

3 | RESULTS

3.1 | Patients' characteristics

One hundred breast cancer patients treated with CT were included (52 ± 11 years; 27 ± 6 kg/m^2) and performed the first visit (pre-CT). Eighty-six patients had a second visit after 8 weeks of CT, and 79 patients had a third visit after CT completion. Seventy-seven patients performed the measurements at the three time points. The reasons for drop-out have been detailed elsewhere.[16] The chemotherapy regimens administered in either the adjuvant setting ($n = 53$) or the neoadjuvant setting ($n = 47$) included anthracycline-cyclophosphamide followed by paclitaxel with or without trastuzumab ($n = 71$), paclitaxel followed by anthracycline-cyclophosphamide ($n = 5$), paclitaxel with or without trastuzumab ($n = 11$) and docetaxel-cyclophosphamide ($n = 13$). The mean duration of CT was 17 ± 5 weeks.

3.2 | Prevalence of CRF and its development trajectories

The prevalence of CRF increased during CT treatment (Table S1). Accordingly, 13 patients were clinically considered fatigued pre-CT (13%), against 39 patients after 8 weeks of treatment (45%) and 43 patients post-CT (54%).

Among the 77 patients who performed the measurements at the three time points, seven patterns of CRF trajectories were identified during treatment (Table 1). These patterns included patients who were fatigued at the three time points ($n = 6$, 8%, pattern 1), fatigued pre-CT and after 8 weeks ($n = 1$, 1%, pattern 2), fatigued after 8 weeks and post-CT ($n = 19$, 25%, pattern 3), fatigued pre- and post-CT ($n = 3$, 4%, pattern 4), fatigued only after 8 weeks ($n = 7$, 9%, pattern 5), fatigued only post-CT ($n = 15$, 19%, pattern 6) and never fatigued ($n = 26$, 34%, pattern 7). Overall, three main patterns (out of 7) explained 78% of the patients' status: never fatigued (34%), fatigued at 8 weeks and post-CT (25%) and fatigued only post-CT (19%). There were no differences pre-CT in patient age or body mass index between the seven CRF trajectories (Table S2). Moreover, there were no differences between the patterns of CRF trajectories (pre-CT, at 8 weeks and post-CT; Table 2) in terms of the 6-MWT distance, muscle mass, knee extensors force, knee neuromuscular fatigue, handgrip force, or physical activity level (please note that pattern 2 was not included in the ANOVA analysis given that there was only one patient, and therefore, no variance). While a pattern effect was found for handgrip neuromuscular fatigue ($p = 0.017$), post hoc analysis did not reveal any differences between the seven identified patterns.

3.3 | Fatigued patients versus non-fatigued patients

The patients' characteristics are presented in Table S1 and did not differ between fatigued and non-fatigued patients at the three time points (i.e., pre-CT, after 8 weeks and post-CT).

3.3.1 | 6-MWT distance

When all patients were investigated together,[16] the 6-MWT distance decreased after 8 weeks of treatment (−2.8%; 540 ± 88 m vs. 525 ± 81 m; $p = 0.021$) and reached −6.7% post-CT (499 ± 77 m; $p < 0.001$). Then, we found a reduced exercise capacity in fatigued patients compared to non-fatigued patients during CT (Table 3, $p = 0.001$). Moreover, a significant difference in the evolution of the 6-MWT distance throughout the CT treatment was detected between fatigued and non-fatigued patients (Figure 1A, group × time interaction effect: $p = 0.034$). More precisely, fatigued patients experienced a greater decrease in the 6-MWT distance compared to non-fatigued patients from pre-CT to 8 weeks (−6.4 ± 12.6% vs. 0.2 ± 8.9%; $p = 0.024$) and from pre- to post-CT (−12.1 ± 9.2% vs. −0.3 ± 11.7%; $p < 0.001$). ROC curve analysis (AUC: 0.69; 95% CI: 0.580.80) revealed that a patient whose 6-MWT distance decreased by more than 2.6% from pre-CT to 8 weeks was at risk of CRF at 8 weeks (sensitivity: 67%; specificity: 64%; $p = 0.003$). ROC curve analysis (AUC: 0.80; 95% CI: 0.700.80) revealed that a patient whose 6-MWT distance decreased by more than 7.0% was at risk of CRF post-CT (sensitivity: 74%; specificity: 70%; $p < 0.001$).

3.3.2 | Physical activity level (GPAQ)

When all patients were investigated together,[16] the physical activity level remained stable throughout the CT treatment. However, fatigued patients had a lower physical activity level compared to non-fatigued patients during the CT treatment (Table 3, $p < 0.001$). No difference was found in the evolution of the physical activity level throughout the CT treatment between fatigued and non-fatigued patients (Figure 1B).

TABLE 1 Trajectories of cancer-related fatigue development during CT treatment.

	Pre-CT	8 weeks	Post-CT	Number of patients, *n* (%)
Always fatigued				
Pattern 1: three time points	×	×	×	6 (8%)
Fatigued at two time points				
Pattern 2: pre-CT and after 8 weeks	×	×		1 (1%)
Pattern 3: after 8 weeks and post-CT		×	×	19 (25%)
Pattern 4: pre- and post-CT	×		×	3 (4%)
Fatigued at one time point				
Pattern 5: after 8 weeks		×		7 (9%)
Pattern 6: post-CT			×	15 (19%)
Never fatigued				
Pattern 7: three time points				26 (34%)

Note: Assessments were made pre-CT, after 8 weeks and post-CT.
Abbreviation: CT, chemotherapy.

TABLE 2 Parameters of exercise capacity, neuromuscular fatigue, and force between the 7 trajectories of cancer-related fatigue.

	Pre-CT	8 weeks	Post-CT	Effects (*p*-values) Pattern	Time	Pattern × Time
6-MWT distance, m				0.532	<0.001	<0.001
Pattern 1	528 ± 83	481 ± 147	473 ± 88			
Pattern 2	668 ± 0	630 ± 0	713 ± 0			
Pattern 3	562 ± 77	515 ± 83	479 ± 73			
Pattern 4	480 ± 60	478 ± 97	471 ± 86			
Pattern 5	526 ± 93	536 ± 70	490 ± 65			
Pattern 6	525 ± 64	523 ± 75	423 ± 71			
Pattern 7	536 ± 74	542 ± 67	528 ± 56			
Muscle mass, kg				0.199	<0.001	<0.001
Pattern 1	21.7 ± 3.9	20.9 ± 4.0	21.0 ± 4.0			
Pattern 2	17.3 ± 0	17.4 ± 0	17.0 ± 0			
Pattern 3	18.5 ± 3.5	18.1 ± 3.9	17.9 ± 4.0			
Pattern 4	21.3 ± 3.1	20.5 ± 2.6	19.9 ± 3.5			
Pattern 5	18.7 ± 5.2	18.2 ± 5.2	18.2 ± 5.2			
Pattern 6	19.7 ± 2.8	19.8 ± 2.8	19.8 ± 2.7			
Pattern 7	18.3 ± 2.9	17.9 ± 3.1	17.9 ± 3.1			
Knee extensors muscle force, *N*				0.225	<0.001	0.5945
Pattern 1	374 ± 102	326 ± 65	332 ± 100			
Pattern 2	371 ± 0	320 ± 0	387 ± 0			
Pattern 3	298 ± 89	283 ± 83	277 ± 83			
Pattern 4	368 ± 92	340 ± 97	332 ± 80			
Pattern 5	264 ± 51	248 ± 32	250 ± 42			
Pattern 6	310 ± 92	305 ± 97	286 ± 98			
Pattern 7	319 ± 72	316 ± 72	308 ± 65			
Handgrip muscle force, *N*				0.338	0.030	0.105
Pattern 1	266 ± 71	262 ± 43	258 ± 57			
Pattern 2	224 ± 0	221 ± 0	203 ± 0			
Pattern 3	240 ± 54	239 ± 52	228 ± 53			
Pattern 4	292 ± 59	253 ± 38	303 ± 6			
Pattern 5	234 ± 51	209 ± 39	220 ± 64			
Pattern 6	255 ± 39	250 ± 36	244 ± 37			
Pattern 7	247 ± 48	249 ± 52	243 ± 48			
Knee extensors neuromuscular fatigue, %				0.096	0.318	0.633
Pattern 1	−28.2 ± 9.2	−25.2 ± 7.9	−25.8 ± 6.0			
Pattern 2	−30.7 ± 0	−25.6 ± 0	−40.8 ± 0			
Pattern 3	−21.0 ± 6.7	−23.0 ± 4.0	−23.2 ± 7.3			
Pattern 4	−20.5 ± 6.3	−26.3 ± 14.7	−22.0 ± 12.6			
Pattern 5	−19.9 ± 4.1	−21.7 ± 4.9	−17.4 ± 4.4			
Pattern 6	−20.2 ± 5.6	−22.2 ± 6.8	−23.2 ± 6.8			
Pattern 7	−20.1 ± 5.7	−21.0 ± 6.9	−19.7 ± 4.8			
Handgrip neuromuscular fatigue, %				0.017	0.073	0.447
Pattern 1	−35.7 ± 8.5	−41.0 ± 9.4	−39.7 ± 9.9			
Pattern 2	−40.8 ± 0	−25.3 ± 0	−29.0 ± 0			
Pattern 3	−31.7 ± 7.8	−39.4 ± 13.6	−33.5 ± 11.2			
Pattern 4	−23.2 ± 14.5	−26.8 ± 14.7	−25.7 ± 4.7			

(Continues)

TABLE 2 (Continued)

	Pre-CT	8 weeks	Post-CT	Effects (*p*-values) Pattern	Time	Pattern × Time
Pattern 5	−26.6 ± 11.0	−25.4 ± 10.6	−28.2 ± 7.2			
Pattern 6	−25.9 ± 7.2	−31.2 ± 7.6	−30.7 ± 7.8			
Pattern 7	−32.0 ± 8.7	−32.8 ± 10.5	−31.1 ± 9.7			
Physical activity level, MET-min/week				0.096	0.872	0.041
Pattern 1	507 ± 418	357 ± 469	753 ± 1190			
Pattern 2	1680 ± 0	2460 ± 0	1000 ± 0			
Pattern 3	1076 ± 1164	631 ± 837	673 ± 933			
Pattern 4	573 ± 560	1627 ± 2162	260 ± 242			
Pattern 5	791 ± 630	554 ± 650	1066 ± 655			
Pattern 6	1376 ± 799	1293 ± 799	977 ± 863			
Pattern 7	953 ± 754	1297 ± 1102	1608 ± 1488			

Note: Assessments were made pre-CT, after 8 weeks and post-CT. The data are presented as the means ± SDs. 6-MWT, 6-min walking test; CT, chemotherapy. Pattern 1: patients who were fatigued at the three time points ($n = 6$); Pattern 2: patients who were fatigued pre-CT and after 8 weeks ($n = 1$); Pattern 3: patients who were fatigued after 8 weeks and post-CT ($n = 19$); Pattern 4: patients who were fatigued pre- and post-CT ($n = 3$); Pattern 5: patients who were fatigued only after 8 weeks ($n = 7$); Pattern 6: patients who were fatigued only post-CT ($n = 15$); Pattern 7: patients who were never fatigued ($n = 26$).

TABLE 3 Parameters of exercise capacity, neuromuscular fatigue, and force during CT treatment between non-fatigued and fatigued patients.

	Pre-CT Non-fatigued *n* = 87 Fatigued *n* = 13	8 weeks Non-fatigued *n* = 47 Fatigued *n* = 39	Post-CT Non-fatigued *n* = 36 Fatigued *n* = 43	Effects (*p*-values) Group	Time	Group × Time
6-MWT distance, m				0.001	0.136	0.316
Non-fatigued	545 ± 74	534 ± 74	531 ± 70			
Fatigued	506 ± 152	514 ± 90	472 ± 72			
Physical activity level, MET-min/week				<0.001	0.430	0.938
Non-fatigued	1151 ± 1233	1290 ± 1062	1460 ± 1337			
Fatigued	606 ± 588	598 ± 750	761 ± 912			
Muscle mass, kg				0.078	0.215	0.302
Non-fatigued	18.8 ± 3.2	18.7 ± 3.0	18.1 ± 3.4			
Fatigued	20.5 ± 3.3	18.7 ± 3.8	19.2 ± 3.6			
Knee extensors muscle force, *N*				0.837	0.080	0.074
Non-fatigued	313 ± 81	321 ± 89	303 ± 67			
Fatigued	350 ± 103	288 ± 75	292 ± 90			
Handgrip muscle force, *N*				0.885	0.288	0.147
Non-fatigued	250 ± 50	254 ± 48	237 ± 52			
Fatigued	260 ± 72	234 ± 48	243 ± 49			
Knee extensors neuromuscular fatigue, %				<0.001	0.027	0.118
Non-fatigued	−21.0 ± 6.4	−21.5 ± 7.9	−19.4 ± 4.8			
Fatigued	−28.9 ± 11.2	−24.1 ± 6.4	−23.5 ± 7.1			
Handgrip neuromuscular fatigue, %				0.009	0.205	0.627
Non-fatigued	−30.5 ± 8.2	−31.8 ± 9.5	−30.5 ± 8.9			
Fatigued	−34.8 ± 11.3	−36.8 ± 12.4	−32.8 ± 10.0			

Note: Assessments were made pre-CT, after 8 weeks and post-CT. Patients were classified as clinically fatigued if they scored ≤34 and non-fatigued if they scored >34 on the FACIT-F questionnaire. The data are presented as the means ± SDs. Significant differences from non-fatigued patients. 6-MWT, 6-min walking test.
Abbreviation: CT, chemotherapy.

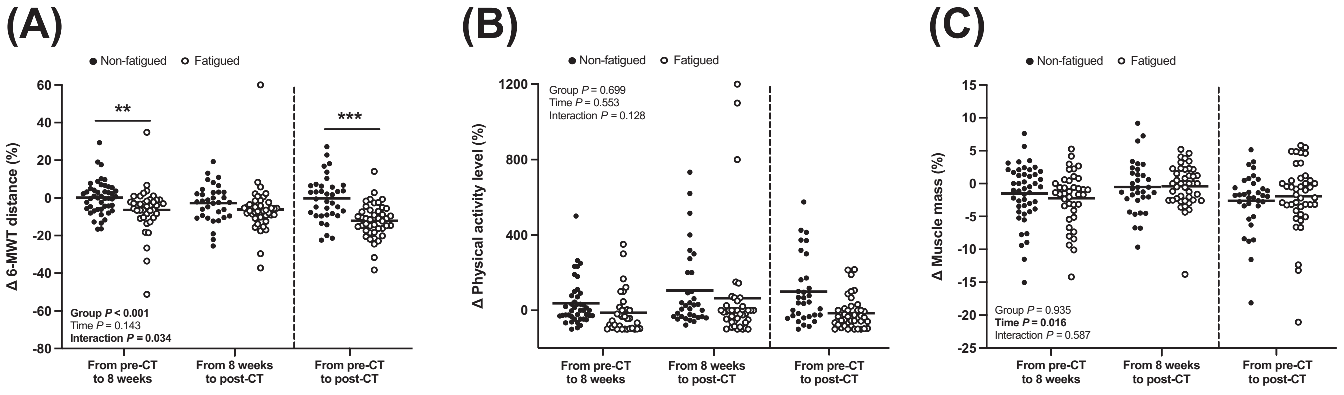

FIGURE 1 The evolution of the 6-MWT distance (A), physical activity level (B) and muscle mass (C) during CT treatment in non-fatigued (black) and fatigued (white) patients with breast cancer. Analyses were performed from pre-CT to 8 weeks (non-fatigued: $n = 39$ and fatigued: $n = 47$), from 8 weeks to post-CT (non-fatigued: $n = 43$ and fatigued: $n = 36$) and from pre- to post-CT (non-fatigued: $n = 43$ and fatigued: $n = 36$). Each patient was allocated to the fatigued versus non-fatigued group according to her FACIT-F score obtained at the last time point (i.e. at 8 weeks for the pre-8 weeks evolution and at post-CT for the 8 weeks-post-CT and pre-post-CT evolutions). The means are represented with horizontal black lines. CT, chemotherapy.

3.3.3 | Muscle mass

When all patients were investigated together,[16] a decrease in skeletal muscle mass (−2.3%, $p = 0.002$) was found post-CT, which occurred within the first 8 weeks of CT treatment ($p < 0.001$). Muscle mass did not differ between fatigued and non-fatigued patients (Table 3). Moreover, no difference was found in the evolution of muscle mass throughout the CT treatment between fatigued and non-fatigued patients (Figure 1C).

3.3.4 | Muscle force

When all patients were investigated together,[16] the knee extensor muscle force decreased within the first 8 weeks of treatment, reaching −4.9% post-CT (318 ± 84 N vs. 297 ± 80 N; $p < 0.001$). Handgrip muscle force also decreased, but this reduction was found only post-CT (251 ± 53 N vs. 241 ± 50 N; $p = 0.001$). The force of the knee extensors and handgrip muscles did not differ between fatigued and non-fatigued patients throughout the treatment (Table 3). While fatigued patients experienced a greater decrease in their knee extensor force than non-fatigued patients throughout the treatment ($p = 0.050$; Figure 2A), post hoc analysis did not reveal a significant difference at any specific time of the CT treatment. No difference was found in the evolution of the handgrip force throughout the CT treatment between fatigued and non-fatigued patients (Figure 2B).

3.3.5 | Neuromuscular fatigue

When all patients were investigated together,[16] knee extensors and handgrip neuromuscular fatigue remained stable post-CT. Then, a greater knee extensors ($p < 0.001$) and handgrip ($p = 0.009$) neuromuscular fatigue was found in the fatigued group compared to the non-fatigued group during CT (Table 3). No differences in the evolution of knee extensors or handgrip neuromuscular fatigue were found between fatigued and non-fatigued patients throughout the CT treatment (Figure 2C and 2D, respectively).

3.4 | Correlations with cancer-related fatigue (FACIT-F score)

The correlations are presented in Table 4. Pre-CT, only knee extensors neuromuscular fatigue was correlated with the FACIT-F score ($R^2 = 0.14$; $p < 0.001$). After 8 weeks of CT, only the physical activity level was correlated with the FACIT-F score ($R^2 = 0.10$; $p = 0.023$). Post-CT, knee extensors neuromuscular fatigue ($R^2 = 0.12$; $p = 0.002$), physical activity level ($R^2 = 0.08$; $p = 0.011$) and the 6-MWT distance ($R^2 = 0.11$; $p = 0.002$) were correlated with the FACIT-F score. We then performed multiple regressions with the significant parameters. First, 19% of the variance in the FACIT-F score post-CT was explained by the 6-MWT distance ($\beta = 0.04$; SE $= 0.01$; $p = 0.013$) and knee extensors neuromuscular fatigue ($\beta = 0.44$; SE $= 0.17$; $p = 0.012$). By adding the physical activity level in the model, 24% of the variance in the FACIT-F score post-CT was explained (6-MWT distance: $\beta = 0.03$; SE $= 0.01$; $p = 0.030$; knee extensors neuromuscular fatigue: $\beta = 0.44$; SE $= 0.17$; $p = 0.011$; physical activity level: $\beta = 0.002$; SE $= 0.0001$; $p = 0.024$).

In addition to the correlations tested at a specific time point (CT, after 8 weeks and post-CT), we also performed correlations for the evolution of each parameter (Table 4). While no correlations were found from pre-CT to 8 weeks and from 8 weeks to post-CT, evolution from pre- to post-CT correlated with the evolution of the FACIT-F score for the 6-MWT distance ($R^2 = 0.25$; $p < 0.001$), knee extensors force ($R^2 = 0.11$; $p = 0.003$), knee extensors neuromuscular fatigue ($R^2 = 0.12$; $p = 0.002$) and physical activity level ($R^2 = 0.07$; $p = 0.003$). We subsequently tested four models to measure their

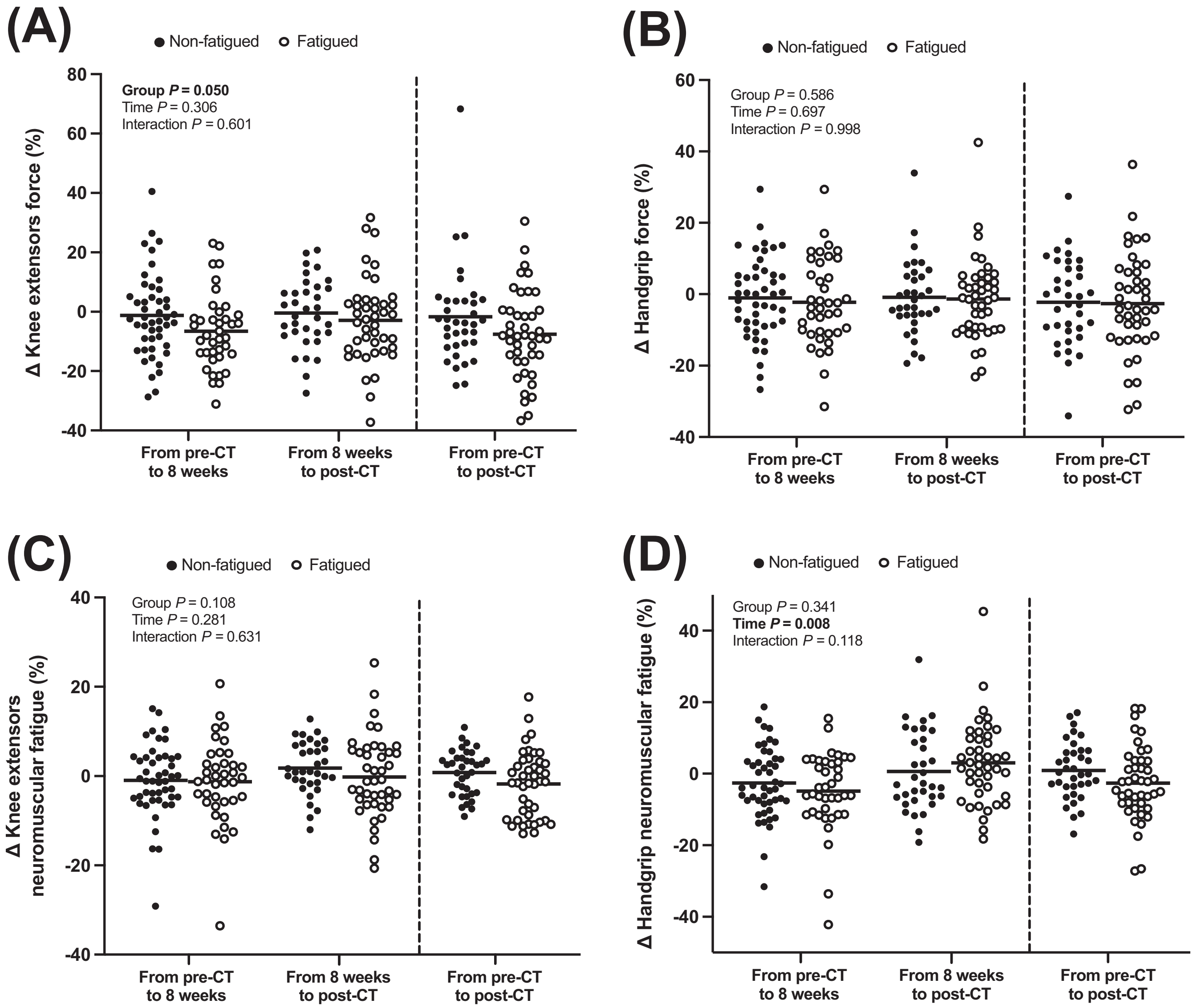

FIGURE 2 The evolution of knee extensors (A) and handgrip (B) muscle force and knee extensors (C) and handgrip (D) neuromuscular fatigue during CT treatment in non-fatigued (black) and fatigued (white) patients with breast cancer. Analyses were performed from pre-CT to 8 weeks (non-fatigued: $n = 39$ and fatigued: $n = 47$), from 8 weeks to post-CT (non-fatigued: $n = 43$ and fatigued: $n = 36$) and from pre- to post-CT (non-fatigued: $n = 43$ and fatigued: $n = 36$). Each patient was allocated to the fatigued versus non-fatigued group according to her FACIT-F score obtained at the last time point (i.e. at 8 weeks for the pre-8 weeks evolution and at post-CT for the 8 weeks-post-CT and pre-post-CT evolutions). The means are represented with horizontal black lines. CT, chemotherapy.

associations with the FACIT-F score evolution from pre- to post-CT. First, the evolution of knee extensors neuromuscular fatigue ($\beta = 0.96$; SE $= 0.35$; $p = 0.007$) and the 6-MWT distance ($\beta = 0.88$; SE $= 0.19$; $p < 0.001$) explained 31% of the variance in the evolution of the FACIT-F score from pre- to post-CT. By adding the knee extensors force in the model, 34% of the variance in the evolution of the FACIT-F score was explained (knee extensors neuromuscular fatigue: $\beta = 0.96$; SE $= 0.34$; $p = 0.006$; 6-MWT distance: $\beta = 0.76$; SE $= 0.20$; $p < 0.001$; knee extensors force: $\beta = 0.26$; SE $= 0.15$; $p = 0.087$). Moreover, the associations of knee extensors neuromuscular fatigue ($\beta = 0.96$; SE $= 0.3$; $p = 0.009$), the 6-MWT distance ($\beta = 0.88$; SE $= 0.19$; $p < 0.001$) and the physical activity level ($\beta = 0.03$; SE $= 0.01$; $p = 0.026$) explained 36% of the variance in the FACIT-F score evolution from pre- to post-CT. Finally, combining the knee extensors neuromuscular fatigue ($\beta = 0.97$; SE $= 0.35$; $p = 0.007$), the 6-MWT distance ($\beta = 0.74$; SE $= 0.21$; $p < 0.001$), the knee extensors force ($\beta = 0.27$; SE $= 0.15$; $p = 0.081$) and the physical activity level ($\beta = 0.03$; SE $= 0.01$; $p = 0.029$) in the model explained 39% of the variance in the FACIT-F score evolution from pre- to post-CT.

4 | DISCUSSION

The aim of this cohort study was to examine the kinetics of CRF evolution throughout CT treatment in patients with breast cancer and to

TABLE 4 Correlations between FACIT-F scores and exercise-related variables during CT.

	Time points			Evolution (Δ)		
	Pre-CT	8 weeks	Post-CT	From pre-CT to 8 weeks	From 8 weeks to post-CT	From pre-CT to post-CT
Explanatory variables						
6-MWT distance	$R^2 = 0.02$ $p = 0.154$	$R^2 = 0.01$ $p = 0.477$	$R^2 = 0.11$ $p = 0.002$	$R^2 = 0.03$ $p = 0.114$	$R^2 = 0.001$ $p = 0.934$	$R^2 = 0.25$ $p < 0.001$
Muscle mass	$R^2 = 0.04$ $p = 0.055$	$R^2 = 0.04$ $p = 0.576$	$R^2 = 0.01$ $p = 0.343$	$R^2 = 0.00$ $p = 0.935$	$R^2 = 0.01$ $p = 0.306$	$R^2 = 0.00$ $p = 0.990$
Knee extensors force	$R^2 = 0.01$ $p = 0.330$	$R^2 = 0.02$ $p = 0.250$	$R^2 = 0.03$ $p = 0.312$	$R^2 = 0.004$ $p = 0.554$	$R^2 = 0.002$ $p = 0.673$	$R^2 = 0.11$ $p = 0.003$
Handgrip force	$R^2 = 0.0004$ $p = 0.830$	$R^2 = 0.02$ $p = 0.207$	$R^2 = 0.001$ $p = 0.825$	$R^2 = 0.002$ $p = 0.709$	$R^2 = 0.04$ $p = 0.084$	$R^2 = 0.003$ $p = 0.652$
Knee extensors neuromuscular fatigue	$R^2 = 0.14$ $p < 0.001$	$R^2 = 0.04$ $p = 0.065$	$R^2 = 0.12$ $p = 0.002$	$R^2 = 0.02$ $p = 0.165$	$R^2 = 0.003$ $p = 0.623$	$R^2 = 0.12$ $p = 0.002$
Handgrip neuromuscular fatigue	$R^2 = 0.01$ $p = 0.260$	$R^2 = 0.02$ $p = 0.166$	$R^2 = 0.02$ $p = 0.272$	$R^2 = 0.01$ $p = 0.297$	$R^2 = 0.01$ $p = 0.385$	$R^2 = 0.04$ $p = 0.090$
Physical activity level	$R^2 = 0.03$ $p = 0.091$	$R^2 = 0.10$ $p = 0.023$	$R^2 = 0.08$ $p = 0.011$	$R^2 = 0.04$ $p = 0.095$	$R^2 = 0.01$ $p = 0.360$	$R^2 = 0.07$ $p = 0.003$
Models						
Knee extensors neuromuscular fatigue	–	–	$p = 0.012$	–	–	$p = 0.007$
6-MWT distance	–	–	$p = 0.013$	–	–	$p < 0.001$
	–	–	$R^2 = 0.19$	–	–	$R^2 = 0.31$
Knee extensors neuromuscular fatigue	–	–	–	–	–	$p = 0.006$
6-MWT distance	–	–	–	–	–	$p < 0.001$
Knee extensors force	–	–	–	–	–	$p = 0.087$
						$R^2 = 0.34$
Knee extensors neuromuscular fatigue	–	–	$p = 0.011$	–	–	$p = 0.009$
6-MWT distance	–	–	$p = 0.030$	–	–	$p < 0.001$
Physical activity level	–	–	$p = 0.024$	–	–	$p = 0.026$
	–	–	$R^2 = 0.24$	–	–	$R^2 = 0.36$
Knee extensors neuromuscular fatigue	–	–	–	–	–	$p = 0.007$
6-MWT distance	–	–	–	–	–	$p < 0.001$
Knee extensors force	–	–	–	–	–	$p = 0.081$
Physical activity level	–	–	–	–	–	$p = 0.029$
	–	–	–	–	–	$R^2 = 0.39$

Note: Assessments were made pre-CT, after 8 weeks and post-CT.
Abbreviations: CT, chemotherapy; FACIT-F, functional assessment of chronic illness therapy-fatigue.

determine its relationship with neuromuscular fatigue and exercise capacity. Based on the dissociation between fatigued versus non-fatigued patients throughout the CT treatment, we demonstrated that exercise capacity (assessed via the 6-MWT distance) and knee extensors neuromuscular fatigue were altered in fatigued patients, leading to a reduction in their physical activity level. Interestingly, we also documented seven distinct patterns of CRF trajectories, with three typical patterns representing 78% of the patients' CRF status: patients never fatigued (34%), patients fatigued at 8 weeks and post-CT (25%) and patients fatigued only post-CT (19%). We then built a model that explained 39% of the variance in CRF evolution via the 6-MWT distance, knee extensors force, knee extensors neuromuscular fatigue, and physical activity level.

4.1 | *Exercise capacity and neuromuscular fatigue are reduced in fatigued versus non-fatigued patients with breast cancer*

Owing to the dissociation between fatigued and non-fatigued patients, we demonstrated that exercise capacity was reduced in fatigued patients throughout the CT treatment. Moreover, we also found a correlation between the CRF and exercise capacity (using the 6-MWT distance) post-CT. This relationship between CRF and exercise capacity in breast cancer patients during treatment is supported by previous investigations performed in cancer survivors.[19,20,25] Using a longitudinal approach, the present study revealed that the relationship between CRF and exercise capacity is robust and not limited to transversal observations.[23–25]

Indeed, we identified that the reduction in the 6-MWT distance was greater in fatigued versus non-fatigued patients from pre-CT to 8 weeks and from pre- to post-CT. More precisely, a patient who lost more than 2.6% of the 6-MWT distance from pre-CT to 8 weeks and more than 7.0% from pre- to post-CT was at risk of CRF. Therefore, patients presenting a decrease in exercise capacity should receive specific attention for managing CRF (see *4.4 Clinical applications* for details).

While it is challenging to demonstrate acause-and-effect relationship between CRF and exercise capacity, the existence of a vicious cycle has been postulated,[34,35] where a weak exercise capacity would lead to physical difficulties in daily living tasks, strengthening inactivity[36–38] and physical deconditioning,[34,35] which would ultimately increase CRF.[19] This vicious cycle is further supported by the observation of lower physical activity levels throughout the CT in fatigued patients compared to their non-fatigued counterparts (Table 3) and by greater neuromuscular fatigue in both knee extensors and handgrip muscles in fatigued versus non-fatigued patients (Figure 2). Notably, the greater neuromuscular fatigue observed during treatment in the present study occurred several months or years after treatment in cancer survivors.[23–25]

While fatigued cancer patients developed greater neuromuscular fatigue than non-fatigued patients, no between-group differences were found in knee extensors or handgrip muscle force. This discrepancy between parameters highlights the need not only to assess exclusively maximal muscle force but also to quantify neuromuscular fatigue to predict CRF. This observation is also supported by the consequences of neuromuscular fatigue on the capacity to perform daily living activities.[39] Mechanistically, greater neuromuscular fatigue stems from central (i.e., failure of the central nervous system to voluntarily activate the muscle) and/or peripheral origins (i.e., biochemical changes within the active muscle leading to an attenuated response to neural output).[40] Our group recently reported that patients with breast cancer post-CT developed greater central fatigue during exercise compared to their healthy counterparts,[30] while peripheral fatigue was similar. However, there was no comparison between fatigued and non-fatigued patients. Future studies should focus on the central and peripheral mechanisms of neuromuscular fatigue to determine the impairment site(s) leading to CRF. This is important, as a recent study demonstrated that 'global' neuromuscular fatigue (i.e., no dissociation between central and peripheral fatigue) was related to CRF severity in survivors from various cancers but failed to identify differences in either central or peripheral fatigue between fatigued and non-fatigued patients.[25]

4.2 | CRF trajectories and predictions during CT treatment

The present study revealed that the CRF prevalence increased throughout CT treatment, reaching 54% post-CT. More precisely, seven patterns of CRF trajectories were identified, indicating significant heterogeneity in the response to treatment. This result obtained during treatment is supported by a previous study identifying large heterogeneity in CRF trajectories from pre- to 18 months post-treatment in breast cancer patients.[11] That said, from the seven distinct patterns, we identified three typical patterns that represented 78% of the patients' CRF status: never fatigued (34%), fatigued at 8 weeks and post-CT (25%) and fatigued only post-CT (19%). Therefore, we aimed to predict the evolution of CRF based on exercise-related variables. Interestingly, almost a third (31%) of the evolution of the CRF can be explained by the evolution of the 6-MWT distance and knee extensors neuromuscular fatigue. When knee extensors force and physical activity levels were included in the model, 39% of the variance in CRF was explained. Our results obtained in patients during CT treatment strengthen those obtained in cancer survivors[23–25] and support the interest in assessing and improving, as early as possible, the parameters related to exercise capacity and neuromuscular fatigue. This strategy may help reduce the development of CRF and improve patients' quality of life.

4.3 | Limitations

While the model explains 39% of the variance in CRF evolution, it also means that 61% of the variance remains not understood and explained by other factors. Psychosocial factors not investigated in the present study, such as anxiety, depression, and sleep disturbances, were previously identified as predictors of CRF.[24] Indeed, emotional symptoms and perceived sleep disturbances were identified as the strongest predictors of CRF before starting treatment in breast cancer patients.[41] Other predisposing or precipitating factors can also influence the CRF evolution, such as older age, cancer comorbidities, obesity, inflammation, and pain, etc.[42] Taken together, these findings indicate that CRF is a multifactorial symptom[3,18,24,25] that requires a global assessment.[1] Further multidisciplinary studies are needed to characterize the underlying mechanisms involved in its development during treatment.

The identification of seven patterns for CRF trajectories does not only signify heterogeneity in the response to treatment. It is interesting to note that patients were not equally distributed in each pattern. This allowed to identify three typical patterns but also challenges the clinical relevance of atypical (i.e., 'rare') patterns. That said, although pattern 2 represents only 1% of the present cohort, this proportion applied to the ∼2 M new breast cancers diagnosed each year[43] would represent 20,000 patients worldwide yearly.

4.4 | Clinical applications

Given the large heterogeneity in CRF trajectories during CT treatment, regular assessments of CRF are needed in clinical settings. Patients identified as clinically fatigued are more vulnerable, with reduced exercise capacity and greater neuromuscular fatigue than their non-fatigued counterparts. As such, tailored supportive care should be prescribed to this population to counteract CRF. Currently, exercise training has been identified as the most efficient strategy to reduce CRF.[21] Based on our results, improving exercise capacity and neuromuscular force/fatigue in fatigued patients is essential. To this end, the combination of aerobic exercise with resistance training may be a promising strategy to fight CRF, targeting both exercise capacity and neuromuscular force/fatigue.[22,44]

4.5 | Conclusions

The present cohort study revealed significant heterogeneity in CRF trajectories throughout CT treatment in patients with breast cancer. Indeed, we identified seven distinct patterns leading to three typical patterns representing 78% of the fatigued patients. The dissociation between fatigued and non-fatigued patients highlighted that CRF is associated with altered exercise capacity and neuromuscular fatigue, and a lower physical activity level. Moreover, our results identified the need not only to assess muscle force, but also muscle fatigue. We also built a model that explained 39% of the variance in CRF evolution based on four key parameters, namely, the knee extensors neuromuscular fatigue, 6-MWT distance, knee extensors force, and physical activity level. Thus, exercise training, one of the most effective strategies for reducing CRF, should be initiated at the start of CT treatment, and improvements in both exercise capacity and neuromuscular force and fatigue should be prioritized.

AUTHOR CONTRIBUTIONS

Joris Mallard: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; data curation; software; formal analysis; project administration. **Elyse Hucteau:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; data curation; project administration. **Roland Schott:** Conceptualization; validation; supervision; resources; methodology; writing – review and editing. **Xavier Pivot:** Conceptualization; methodology; validation; writing – review and editing; supervision; resources. **Allan F. Pagano:** Conceptualization; funding acquisition; methodology; validation; writing – review and editing; supervision; resources. **Thomas J. Hureau:** Conceptualization; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The protocol was approved by the French Ethics Committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, number ID RCB: 2019-A00848-49). All the subjects provided written informed consent in accordance with the Declaration of Helsinki.

The study has been registered on Clinical Trial (NCT03956641).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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