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## ORIGINAL ARTICLE

# Early skeletal muscle deconditioning and reduced exercise capacity during (neo)adjuvant chemotherapy in patients with breast cancer

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## Abstract

**Background:** Fatigue is a hallmark of breast cancer and is associated with skeletal muscle deconditioning. If cancer-related fatigue occurs early during chemotherapy (CT), the development of skeletal muscle deconditioning and its effect on exercise capacity remain unclear. The aim of this study was to investigate the evolution of skeletal muscle deconditioning and exercise capacity in patients with early-stage breast cancer during CT.

**Methods:** Patients with breast cancer had a visit before undergoing CT, at 8 weeks, and at the end of chemotherapy (post-CT). Body composition was determined through bioelectrical impedance analysis. Knee extensor, handgrip muscle force and fatigue was quantified by performing maximal voluntary isometric contractions and exercise capacity using the 6-min walking test. Questionnaires were also administered to evaluate quality of life, cancer-related fatigue, and physical activity level.

**Results:** Among the 100 patients, reductions were found in muscle mass (−2.3%,  $p = .002$ ), exercise capacity (−6.7%,  $p < .001$ ), and knee extensor force (−4.9%,  $p < .001$ ) post-CT, which occurred within the first 8 weeks of treatment with no further decrease thereafter. If muscle fatigue did not change, handgrip muscle force decreased post-CT only (−2.5%,  $p = .001$ ), and exercise capacity continued to decrease between 8 weeks and post-CT (−4.6%,  $p < .001$ ). Quality of life and cancer-related fatigue were impaired after 8 weeks ( $p < .001$ ) and remained stable thereafter, whereas the physical activity level remained stable during chemotherapy.

Joris Mallard and Elyse Hucteau contributed equally to this work.

Thomas J. Hureau and Allan F. Pagano contributed equally to this work.

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**Conclusions:** Similar to cancer-related fatigue, skeletal muscle deconditioning and reduced exercise capacity occurred early during breast cancer CT. Thus, it appears essential to prevent these alterations through exercise training implemented during CT.

**KEYWORDS**

cancer-related fatigue, exercise capacity, muscle atrophy, muscle fatigue, muscle force

## INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide,<sup>1</sup> and chemotherapy (CT) is extensively administered to treat this disease. However, CT is not devoid of side effects such as chronic fatigue,<sup>2</sup> defined as a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning and is not fully reversed by rest.<sup>3,4</sup> Specifically, cancer-related fatigue is a highly prevalent symptom<sup>5</sup> that is frequently experienced from CT initiation<sup>6,7</sup> and can persist for years after treatment completion.<sup>8</sup>

Mechanistically, cancer-related fatigue is associated with skeletal muscle deconditioning, which is defined as a direct consequence of global muscle homeostasis perturbation, leading to a decrease in muscle mass and/or force, as well as an increase in muscle fatigue.<sup>9,10</sup> It is known that both cancer-related fatigue and skeletal muscle deconditioning represent major actors in a vicious cycle in which cancer-related fatigue leads to a reduction in daily physical activity, resulting in skeletal muscle deconditioning that reinforces fatigue again.<sup>11,12</sup> This vicious cycle leads to a decrease in exercise capacity<sup>9</sup> and diminishes the quality of life<sup>6</sup> of patients with breast cancer. However, although cancer-related fatigue increased quickly after the start of the CT (ie, between 2 and 7 days),<sup>13,14</sup> alterations in the previously mentioned parameters were only documented post-CT or even later in cancer survivors.<sup>15–20</sup>

A better characterization of skeletal muscle deconditioning development in patients with breast cancer undergoing CT will help in determining the optimal timing to implement efficient prevention strategies, such as exercise training interventions. In this context, the aim of the present study was to investigate the development of cancer-related fatigue, skeletal muscle deconditioning, and exercise capacity. We hypothesized that patients with breast cancer would experience, in parallel to the well-described increase in cancer-related fatigue, early skeletal muscle deconditioning and reduced exercise capacity during CT treatment.

## METHODS

### Participants and study design

We previously published the full description of the study design and assessments used in this cohort clinical study.<sup>11</sup> Patients with breast cancer from the Institut de Cancérologie Strasbourg Europe were

included in the PROTECT-01 study (NCT03956641). All patients provided written informed consent before enrollment, and the study was conducted in accordance with the Declaration of Helsinki and ethics approval received from the national ethics committee (2019-A00848-49). The patients had three visits: (1) before the first CT administration (pre-CT), (2) 8 weeks after, and (3) within 2 weeks after CT completion (post-CT). All assessments are detailed here.

The eligibility criteria included nonpregnant women at least 18 years old with a World Health Organization performance status of 0 to 2 who were diagnosed with early-stage breast cancer and treated with (neo)adjuvant CT. Patients were excluded if they had psychiatric, musculoskeletal, or neurological disorders. Note that it was initially planned to include patient cohorts of lung and colorectal metastatic cancer<sup>21</sup> but they were withdrawn because we were not able to recruit them in our hospital.

### Body composition

Body composition was determined using a bioelectrical impedance analysis device (SECA mBCA 515, SECA, Germany).<sup>22</sup> Body mass, lean mass, fat mass, extracellular water, and skeletal muscle mass (total, arm, trunk, leg) were measured. For the arms and legs, the mean between the right and left limbs was calculated. Body composition assessment was performed at the same time of day, in underwear and without water consumption 1 hour before.

### Muscle force

Knee extensor muscle force was assessed in a seated position with the hip and knee joints fixed at 100° and 90°, respectively (where 180° represents a full knee extension) and aligned with the frontal axis. An ergometer connected to a force transducer (Force sensor kit, Chronojump, Spain) was strapped above the ankle to the lower right leg.

The handgrip muscle force was measured using a handgrip dynamometer (Takei, TK200, Takei Scientific Instruments, Japan).<sup>23</sup> 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 a familiarization and a standardized warm-up, patients were asked to perform three 3-s maximal voluntary

isometric contractions under verbal encouragement.<sup>24,25</sup> There was a 30-s rest period between each contraction. The mean value of the three trials was used for further analysis.

## Muscle fatigue

Patients were placed in the same position as in the muscle force assessment. For both knee extensors and handgrip muscles, muscle fatigue was assessed by performing ten 3-s maximal voluntary isometric contractions under verbal encouragement with a 2-s rest period between each contraction. Muscle fatigue was calculated as the percent difference in peak force between the first and the last contraction.<sup>26</sup>

## Exercise capacity

Exercise capacity was assessed using the 6-min walking test.<sup>27</sup> Patients walked alone with no disturbance in a covered, flat, straight, well-delineated, 20-m corridor. Instructions were systematically given to the patient, and the total distance walked during the test (in meters) was used to assess exercise capacity.

## Questionnaires

### Quality of life and perceived fatigue

The European Organization for Research and Treatment of Cancer (EORTC) quality of life core questionnaire 30 items (EORTC QLQ-C30) version 3<sup>28</sup> and the functional assessment of chronic illness therapy – fatigue (FACIT-F) version 4<sup>29</sup> were used to assess the quality of life. For the EORTC QLQ-C30, the questionnaire includes five functioning scales and three symptom scales. Additional cancer symptoms and financial difficulties were also reported by separate items. Higher scores on the global and functioning scales were considered to be better, and a lower score on the symptom scale was considered to be better. A score for each subdomain of the FACIT-F was calculated. Additionally, the fatigue subscale was used to reflect self-reported fatigue. For every scale, higher scores indicate better functioning or less fatigue.

### Physical activity level

Physical activity level was assessed using the 16-item global physical activity questionnaire (GPAQ) version 2.<sup>30</sup> The GPAQ was used to collect information on sedentary behavior and physical activity in three domains (activity at work, travel to and from places, and recreational activities during a typical week). A global score was calculated in metabolic equivalents (min/week), in which the higher the score, the better the patient's physical activity level.

## Sample size calculation and statistical analysis

The sample size calculation, fully described in Mallard et al.,<sup>21</sup> was based on a reduction in 6-min walking test and resulted in 300 patients being included, equally divided into three groups of interest: 100 patients with breast cancer, 100 patients with lung metastatic cancer, and 100 patients with colorectal metastatic cancer. However, as mentioned previously, metastatic cohorts were cancelled, and we

**TABLE 1** Participant characteristics at baseline

Participant characteristics	n = 100
Characteristic (mean ± SD)	
Age (year)	52 ± 11
Body mass (kg)	71 ± 16
Body mass index (kg/m <sup>2</sup> )	27 ± 6
Physical activity level (n)	
Inactive/low	51
Moderate	43
High	6
Performance status WHO (n)	
0	77
1	22
2	1
Grading SBR (n)	
II	46
II to III	13
III	41
Tumor type (n)	
Triple negative	19
Luminal (A/B)	57
HER2-positive	24
Treatment setting (n)	
Adjuvant	53
Neoadjuvant	47
Chemotherapy regimen (n)	
Anthracycline-cyclophosphamide followed by paclitaxel	53
Anthracycline-cyclophosphamide followed by paclitaxel + trastuzumab	18
Paclitaxel followed by anthracycline-cyclophosphamide	5
Paclitaxel	9
Paclitaxel + trastuzumab	2
Docetaxel-cyclophosphamide	13

Abbreviations: HER2, human epidermal growth factor receptor 2; SBR, Scarff-Bloom-Richardson; WHO, World Health Organization performance status.

consequently performed a calculation of the effect size posteriori. Based on the decrease in the 6-min walking test observed post-CT in our cohort of patients with breast cancer, the effect size calculated was 0.95.

Normal distribution of the data was visually checked through QQ plots and was found to be normally distributed for each variable. Homogeneity of variances was then checked with the Levene test. A mixed model analysis of variance (ANOVA) with repeated measures was used to assess the time-course (pre-CT, 8 weeks, and post-CT) of each outcome. Two-way mixed-design ANOVAs with repeated measures (muscle [handgrip vs knee extensors]  $\times$  time [pre-CT, 8 weeks and post-CT]) were used to compare the decline of muscle force according to each muscle group. To compare the effect of the CT administration (adjuvant vs neoadjuvant) and CT regimens (Table 1) on the same outcomes, a two-way mixed design ANOVA (condition  $\times$  time) with repeated measures was used. In case of deviation from sphericity, a Greenhouse-Geisser correction was applied to meet requirements of compound symmetry.

If significant differences were found, multiple comparison analysis was performed with the Tukey post hoc test. Statistical significance was set at  $p < .05$ . Statistical analyses and graphs were made with GraphPad Prism 6 software, and all values are expressed as the mean  $\pm$  SD.

## RESULTS

### Patient characteristics

A total of 147 patients were screened and 100 patients were included in the study (Figure 1). All patients were assessed pre-CT ( $-1 \pm 1$  week before the first chemotherapy administration); their baseline characteristics are shown in Table 1. Eighty-six patients

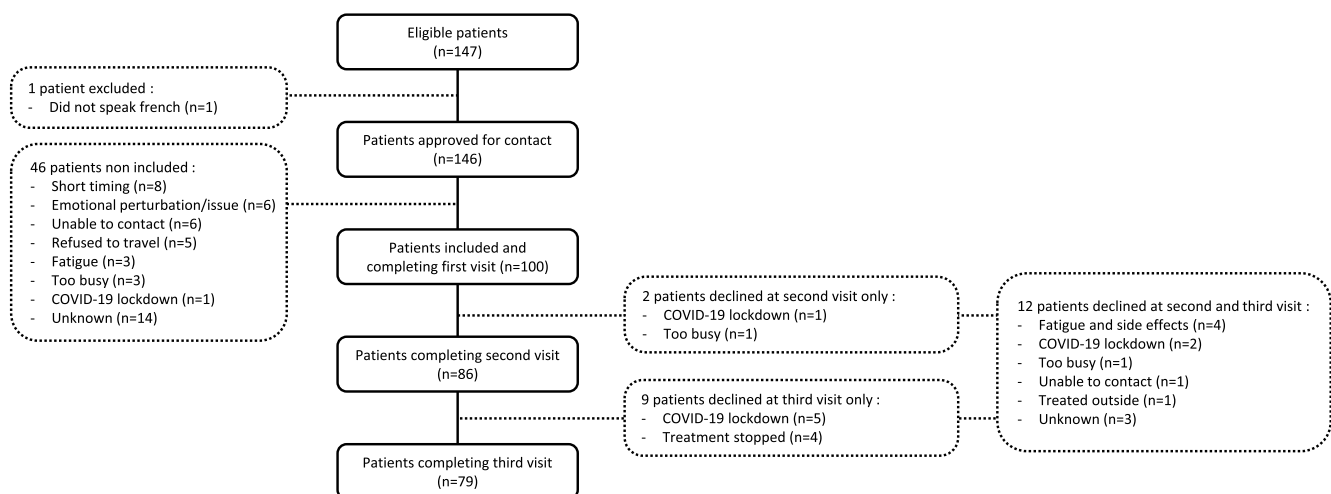
had a second visit after 8 weeks of CT ( $8 \pm 1$  weeks), and 79 patients had a third visit post-CT ( $1 \pm 1$  week after CT completion). More precisely, two patients declined the second visit only, nine declined the third visit only and 12 declined both. Reasons justifying dropouts are reported in Figure 1. The mean CT duration was  $17 \pm 5$  weeks. For all data, there was no specific effect of the CT administrations (ie, adjuvant vs neoadjuvant) or the chemotherapy regimen (Table 1). Consequently, the following results are presented as the mean  $\pm$  SD for all patients regardless of treatment options.

### Skeletal muscle mass

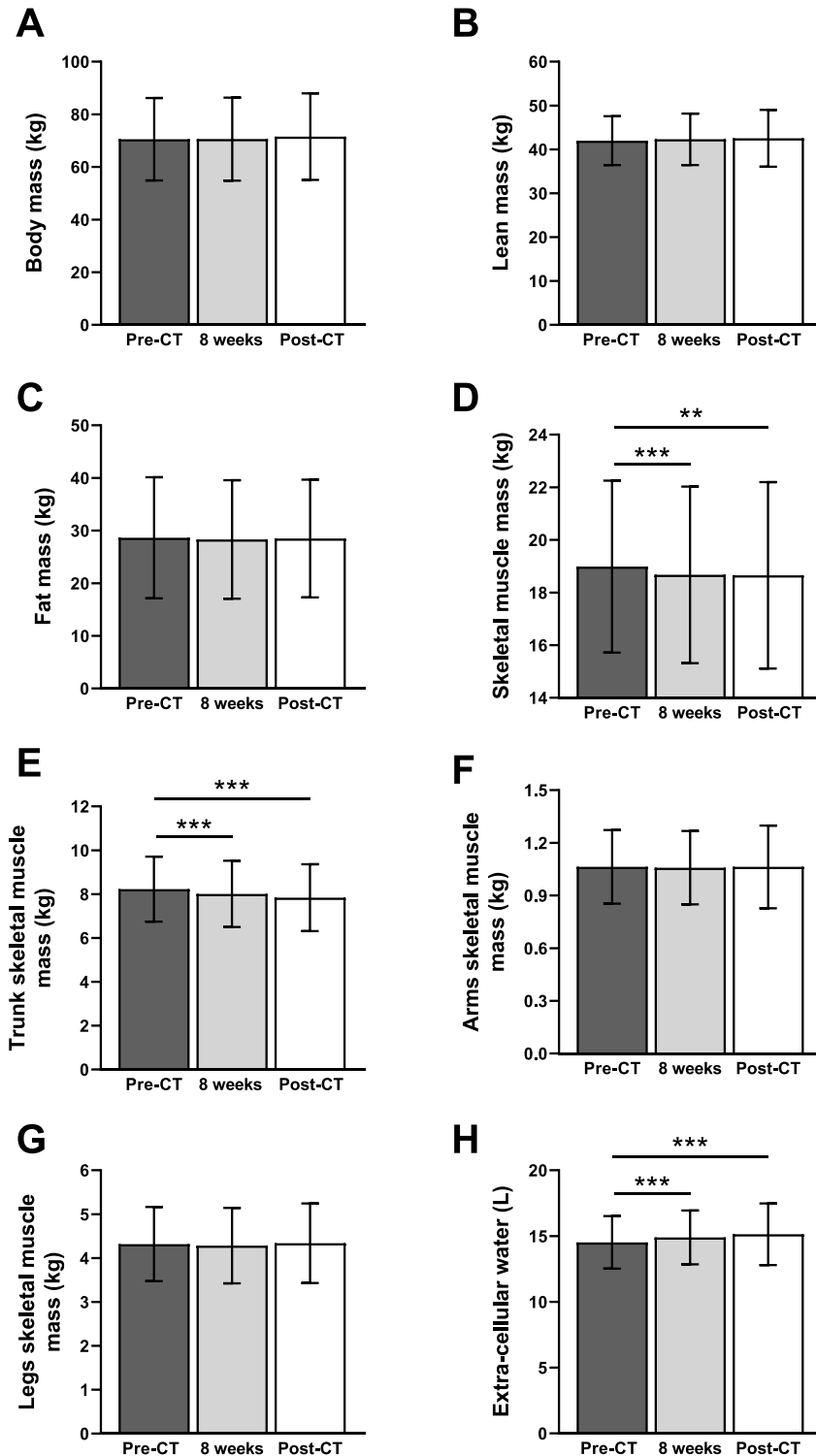
Despite the lack of change in body mass ( $p = .150$ ; Figure 2A), lean mass ( $p = .065$ ; Figure 2B), and fat mass ( $p = .545$ ; Figure 2C) during CT, we found a significant decrease in skeletal muscle mass ( $-2.3\%$ ,  $p = .002$ ; Figure 2D) post-CT, which occurred within the first 8 weeks of CT treatment ( $p < .001$ ) with no further decrease thereafter ( $p = .964$ ). Specifically, this decrease in skeletal muscle mass was mainly located at the trunk level ( $-2.9\%$ ,  $p < .001$ ; Figure 2E), with no change in the arms ( $p = .647$ ; Figure 2F) or legs ( $p = .758$ ; Figure 2G). Finally, an increase in water retention was reported, as evidenced by an increase in extracellular water post-CT ( $+4.4\%$ ,  $p < .001$ ; Figure 2H), which occurred within the first 8 weeks of treatment ( $+2.7\%$ ,  $p < .001$ ).

### Muscle force

As illustrated in Figure 3, the knee extensor force decreased and reached  $-4.9\%$  post-CT ( $318 \pm 84$  N vs  $297 \pm 80$  N,  $p < .001$ ; Figure 3A). This decrease occurred during the first 8 weeks of treatment ( $p = .049$ ) with no further decrease thereafter ( $p = .071$ ).



**FIGURE 1** Flow chart of the participants



**FIGURE 2** Body composition during chemotherapy. Body mass (A), lean mass (B), fat mass (C), skeletal muscle mass (D), trunk skeletal muscle mass (E), arm skeletal muscle mass (F), leg skeletal muscle mass (G), and extracellular water (H) assessed before (pre-CT,  $n = 100$ ), after 8 weeks (8 weeks,  $n = 86$ ), and at the end (post-CT,  $n = 79$ ) of breast cancer CT. All values are expressed as the mean  $\pm$  SD. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . CT, chemotherapy

Handgrip muscle force decreased by 2.5% post-CT only ( $251 \pm 53$  N vs  $241 \pm 50$  N,  $p = .001$ ; Figure 3B). The two-way mixed-design ANOVAs showed significant muscle ( $p < .001$ ) and time ( $p < .001$ ) effect, without interaction effect ( $p = .176$ ).

### Muscle fatigue

No change in muscle fatigue was found post-CT for the knee extensors ( $p = .543$ , Figure 3C), whereas handgrip muscle fatigue

(Figure 3D) increased by 3.6% at 8 weeks ( $p = .019$ ) and returned to baseline values at post-CT measurements ( $p = .745$ ).

### Exercise capacity

As documented in Figure 4, according to the distance achieved during the 6-min walking test, exercise capacity decreased after 8 weeks of CT ( $-2.8\%$ ,  $540 \pm 88$  m vs  $525 \pm 81$  m,  $p = .021$ ) and continued to decrease to reach  $-6.7\%$  post-CT ( $499 \pm 77$  m,  $p < .001$ ).

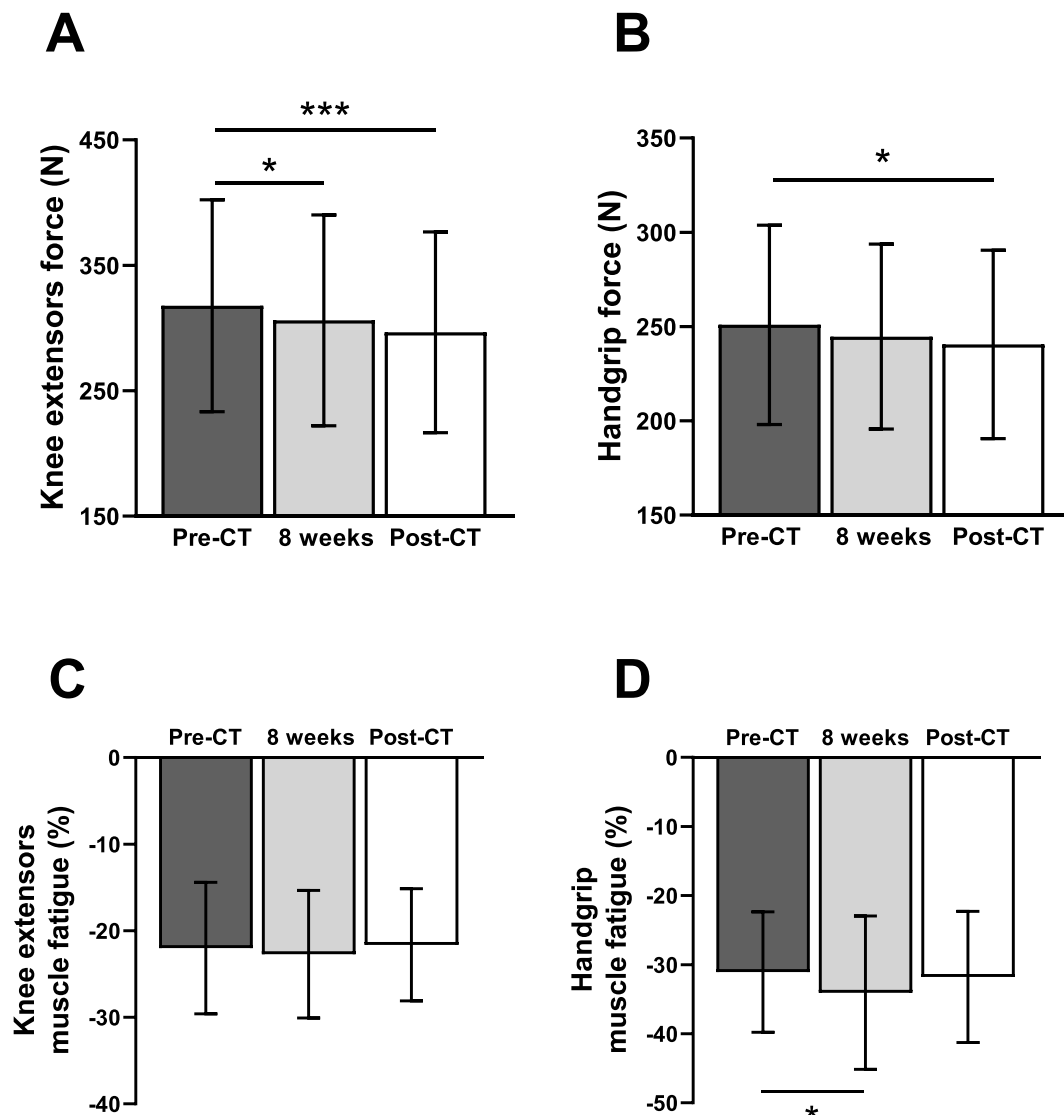
### Questionnaires: Physical activity level, perceived fatigue, and quality of life

The questionnaire scores and  $p$  values are reported in Table 2. The EORTC QLQ-C30 indicated substantial impairments after 8 weeks of

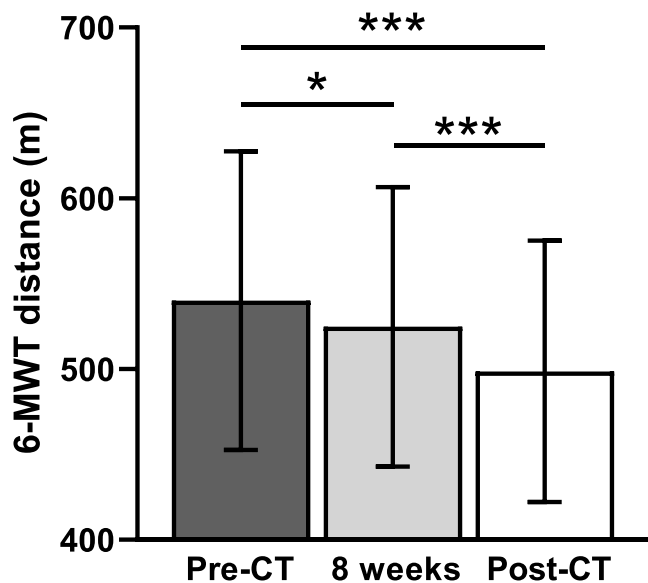
treatment in the global health status, all functional scales, and in the multiple symptom scales (including fatigue and dyspnea), with no further alteration thereafter. Pain increased post-CT, whereas constipation and loss of appetite increased after 8 weeks and then decreased post-CT. The FACIT-F showed alterations in quality of life after 8 weeks of CT, with no further alteration thereafter. More specifically, physical and social well-being decreased after 8 weeks of treatment, whereas emotional well-being improved compared with pre-CT. Using the GPAQ, no change was found in the total physical activity level throughout the treatment.

### DISCUSSION

Thanks to measurements obtained pre-CT, during, and post-CT in patients with early-stage breast cancer, we showed different patterns in the development of cancer-related fatigue, skeletal muscle



**FIGURE 3** Muscle force and fatigue during chemotherapy. Knee extensor (A) and handgrip muscle (B) force and knee extensor (C) and handgrip (D) muscle fatigue assessed before (pre-CT,  $n = 100$ ), after 8 weeks (8 weeks,  $n = 86$ ), and at the end (post-CT,  $n = 79$ ) of breast cancer CT. All values are expressed as the mean  $\pm$  SD. \* $p < .05$ , \*\*\* $p < .001$ . CT, chemotherapy



**FIGURE 4** Exercise capacity during CT. Assessments were performed before (pre-CT,  $n = 100$ ), after 8 weeks (8 weeks,  $n = 86$ ), and at the end (post-CT,  $n = 79$ ) of breast cancer CT. All values are expressed as the mean  $\pm$  SD. \* $p < .05$ , \*\*\* $p < .001$ . 6-MWT, 6-min walking test; CT, chemotherapy.

deconditioning, and exercise capacity. Similar to the questionnaire scores used to assess cancer-related fatigue and quality of life, skeletal muscle mass, knee extensor muscle force, and exercise capacity decreased within the first 8 weeks of treatment, indicating early skeletal muscle deconditioning during CT. Interestingly, only exercise capacity continued to decrease from 8 weeks to the end of treatment, whereas handgrip muscle force was only reduced post-CT, indicating a dissociation between these variables.

### Early skeletal muscle deconditioning during CT

Although previous investigations showed a decrease in skeletal muscle mass post-CT in patients with breast cancer,<sup>19,20</sup> the present study reported that this decrease occurred within the first 8 weeks of treatment with no further changes up to the end of CT. This result highlights the nonlinearity of skeletal muscle atrophy in patients with breast cancer, which is consistent with observations in human models of physical inactivity.<sup>31,32</sup> Of note, the 2.3% reduction in skeletal muscle mass found in the present study at the end of the CT treatment was equivalent to a 12-fold acceleration of the aging process,<sup>33</sup> illustrating the potent toxicity of CT.

In the present study, skeletal muscle mass was quantified by bioelectrical impedance analysis, which dissociated trunk and limb skeletal muscle mass. Our results showed a reduction in trunk muscle mass after 8 weeks of CT and are supported by previous studies conducted in patients with breast cancer.<sup>19,20</sup> Surprisingly, no change in leg muscle mass was observed, whereas it described, using muscle biopsies, a striking reduction in the cross-sectional area of the *vastus lateralis* muscle fibers in patients with breast cancer.<sup>34</sup> Chemotherapy

treatment drastically affects tissue hydration,<sup>35</sup> and it is important to note that the skeletal muscle mass was calculated in our study with the conduction of an electrical signal in skeletal muscle (a water-composed tissue) using bioelectrical impedance analysis. Given the increase in extracellular water observed in our patients, this represents a limitation to the assessment of skeletal muscle mass that we might have overestimated in this specific context.

If a decrease in muscle force is classically observed in patients with breast cancer post-CT,<sup>36,37</sup> we demonstrated that the reduction in knee extensor muscle force occurred within the first 8 weeks of treatment, emphasizing early skeletal muscle deconditioning. With no reduction in leg skeletal muscle mass during CT, the reduction in muscle force is likely explained by neural alterations.<sup>26</sup> In contrast, handgrip muscle force was only decreased post-CT and the decline was lower than that of knee extensors. Together, these results indicate that CT did not similarly affect the upper and lower limb muscle force capacity. Therefore, caution should be taken when using handgrip muscle force as an index of skeletal muscle deconditioning<sup>38</sup> or exercise capacity,<sup>39</sup> whereas knee extensor muscle force might be more insightful as a consequence of their involvement in exercise capacity in older people<sup>40</sup> or patients with cancer.<sup>41</sup>

In contrast to skeletal muscle mass and force, which decreased within the first 8 weeks of treatment and leveled off thereafter, exercise capacity assessed with the 6-min walking test distance decreased linearly throughout CT. If the decrease in knee extensor muscle force contributes to the decrease in exercise capacity within the first 8 weeks, we did not find a correlation between these two variables. In addition, we<sup>42</sup> and others<sup>43</sup> reported a decrease in mitochondrial content post-CT and, given the strong relationship between aerobic capacity and skeletal muscle mitochondrial content,<sup>44</sup> it may also explain the decrease we observed in exercise capacity post-CT. In the absence of change in total physical activity level during the treatment (Table 2), the decrease in muscle mass, muscle force, and exercise capacity was attributed to the CT and its consequences, but likely not to behavioral changes. That said, it is important to note that total physical activity level was assessed using questionnaires and not directly with accelerometry and therefore needs to be interpreted with caution.

### Muscle and perceived fatigue

Similar to the decrease in muscle mass and knee extensor muscle force, perceived fatigue increased drastically within the first 8 weeks of treatment and remained stable thereafter. Consistent with studies in which researchers highlight the relationship between perceived fatigue and quality of life,<sup>7</sup> we also found a reduction in quality of life within the first 8 weeks of treatment. Although our results showed that the development of skeletal muscle deconditioning, cancer-related fatigue and quality of life degradation occurred concomitantly, we also found a linear reduction in exercise capacity throughout chemotherapy. This discrepancy shows the importance of measuring exercise capacity in clinical settings.



**TABLE 2** Cancer-related fatigue, quality of life, and physical activity level during chemotherapy

Outcome variables	Pre-CT (n = 100) Mean ± SD	8 weeks (n = 86) Mean ± SD	Post-CT (n = 79) Mean ± SD	p Values		
				Pre-CT vs 8 wk	8 wk vs post-CT	Pre-CT vs post-CT
EORTC QLQ-C30 questionnaire score						
Functional scales						
Physical functioning	89 ± 14	81 ± 18	79 ± 19	<.001	.634	<.001
Role functioning	91 ± 15	81 ± 21	84 ± 17	<.001	.553	<.004
Emotional functioning	71 ± 21	77 ± 18	74 ± 20	.017	.306	.226
Cognitive functioning	89 ± 18	80 ± 23	79 ± 21	<.001	.936	<.001
Social functioning	88 ± 20	76 ± 27	77 ± 26	<.001	.868	<.001
Symptom scales						
Fatigue	27 ± 21	47 ± 24	50 ± 26	<.001	.523	<.001
Nausea and vomiting	3 ± 8	15 ± 20	10 ± 18	<.001	.171	<.001
Pain	20 ± 24	26 ± 25	32 ± 29	.066	.174	<.001
Dyspnea	12 ± 23	28 ± 29	31 ± 30	<.001	.550	<.001
Insomnia	33 ± 31	36 ± 34	38 ± 34	.539	.911	.376
Loss of appetite	8 ± 18	22 ± 29	14 ± 25	<.001	.016	.074
Constipation	8 ± 20	18 ± 25	16 ± 27	.008	<.001	.053
Diarrhea	7 ± 17	17 ± 26	18 ± 30	.003	.929	.009
Financial difficulties	7 ± 22	11 ± 23	12 ± 25	.143	.671	.072
Global health status	72 ± 15	62 ± 19	61 ± 19	<.001	.973	<.001
FACIT-F questionnaire score						
Quality of life						
Physical well-being	25 ± 3	19 ± 6	19 ± 5	<.001	.999	<.001
Social well-being	22 ± 4	21 ± 4	20 ± 5	.028	.051	<.001
Emotional well-being	17 ± 4	19 ± 4	19 ± 4	<.001	.578	<.001
Functional well-being	19 ± 4	17 ± 4	17 ± 5	<.001	.545	<.001
FACT-G total score	83 ± 11	77 ± 12	75 ± 14	<.001	.316	<.001
Fatigue subscale	43 ± 7	34 ± 10	34 ± 11	<.001	.954	<.001
FACIT-F total score	126 ± 15	111 ± 20	108 ± 23	<.001	.609	<.001
GPAQ questionnaire score						
Physical activity	1080 ± 1181	976 ± 991	1080 ± 1171	.593	.727	.999
Activity at work	139 ± 951	19 ± 181	0 ± 0	.043	.626	.437
Travel to and from places	309 ± 544	166 ± 314	275 ± 452	.034	.121	.885
Recreational activity	632 ± 684	791 ± 933	805 ± 1028	.223	.992	.293
Sedentary behavior	391 ± 157	416 ± 184	422 ± 180	.438	.941	.216

Note: The EORTC QLQ-C30, FACIT-F, and GPAQ questionnaires were administered before (pre-CT, n = 100), after 8 weeks (8 weeks, n = 86), and at the end (post-CT, n = 79) of breast cancer chemotherapy. All values are expressed as the mean ± SD.

Abbreviations: CT, chemotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer (EORTC) quality of life core questionnaire 30 items (QLQ-C30); FACIT, functional assessment of chronic illness therapy - fatigue; FACT-G, functional assessment of cancer therapy - general; GPAQ, global physical activity questionnaire.

In contrast with perceived fatigue, muscle fatigue remained stable post-CT. However, the observation of similar muscle fatigue with respect to lower force capacity post-CT suggests that our patients with breast cancer are not devoid of alterations in muscle fatigue. Indeed, it is a classic observance that weaker individuals develop less muscle fatigue during exercise than their stronger counterparts.<sup>45,46</sup> Therefore, although patients displayed a decrease in maximal force capacity for a given exercise task from pre- to post-CT, they developed similar, and not less, muscle fatigue post-CT. Mechanistically, muscle fatigue has a central and a peripheral origin,<sup>47</sup> and it has already been reported in other contexts that no change in “global” muscle fatigue can still be associated with alterations in central fatigue.<sup>48,49</sup> Using noninvasive measurement methods,<sup>50</sup> further studies investigating central and peripheral fatigue in patients with breast cancer are needed.

## Perspectives for clinical rehabilitation

Based on the early skeletal muscle deconditioning and the decrease in exercise capacity we have documented, preventive strategies such as exercise should be initiated from the beginning of CT treatment and not after, which is how it has been commonly performed.<sup>51</sup> Indeed, it might be more interesting to prevent these side effects and to preserve patients' quality of life<sup>52</sup> with exercise interventions during CT, instead of trying to recover from these side effects afterward.

In the present study, we assessed the consequences of both the disease and the associated side effects of the treatment. Therefore, it was not possible to isolate the effects of the disease vs the treatments on our measures. Regardless, it was more important to characterize the combined effect of these two stressors on the physical function of patients with breast cancer because this is ultimately what rehabilitation programs will have to counteract simultaneously.

## Conclusion

Although the focus of many oncology studies has been on exercise training interventions in cancer survivors with the intention of reversing the negative side effects of treatment, we highlight that skeletal muscle deconditioning and decrease in exercise capacity appeared early in (neo)adjuvant CT treatment in patients with breast cancer. Thus, these findings suggest that it might be interesting to prevent these side effects from occurring rather than trying to recover from them afterward.

## AUTHOR CONTRIBUTIONS

**Joris Mallard:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft preparation, writing – review and editing, visualization, and funding acquisition. **Elyse Hucteau:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources,

data curation, writing – original draft preparation, writing – review and editing, visualization, and funding acquisition. **Roland Schott:** Conceptualization, validation, investigation, writing – review and editing, supervision, project administration, and funding acquisition. **Philippe Trens:** Investigation and writing – review and editing. **Carole Pflumio:** Investigation and writing – review and editing. **Michal Kalish-Weindling:** Investigation and writing – review and editing. **Fabrice Favret:** Methodology, writing – review and editing, and supervision. **Xavier Pivot:** Conceptualization, validation, investigation, writing – review and editing, supervision, project administration, and funding acquisition. **Thomas J. Hureau:** Conceptualization, methodology, validation, writing – original draft preparation, writing – review and editing, visualization, supervision, and funding acquisition. **Allan F. Pagano:** Conceptualization, methodology, validation, writing – original draft preparation, writing – review and editing, visualization, supervision, and funding acquisition.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The funders had no role in the design, execution, interpretation, or writing of the study.

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