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Original Research

Impact of radiation therapy on fatigue at 1 year in breast cancer survivors in the prospective multicentre CANcer TOxicity cohort

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KEYWORDS
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Internal mammary chain;
Quality of life

Abstract ***Background:*** Fatigue is a common and disabling symptom after breast cancer (BC) treatment, significantly impacting patients' quality of life. We aimed to assess the impact of radiation therapy (RT) modalities on fatigue one year after treatment among patients with early-stage BC.

Methods: We used CANTO-RT, a subcohort of CANcer TOxicity (CANTO; NCT01993498), a multicentric nationwide prospective cohort of stages I–III BC treated from 2012 to 2017. Our primary outcome was severe global fatigue 1 year after RT completion (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 score ≥40/100). The secondary outcomes included severe physical, emotional and cognitive fatigue (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-FA12). RT-related variables were used as independent variables. Multivariable logistic regression models assessed associations between RT-related variables and fatigue.

Results: The final analytic cohort included 3295 patients. The prevalence of severe global fatigue 1 year after treatment was 33.3%. Internal mammary chain RT (adjusted odds ratio [OR] 1.48 [95% confidence interval [CI] 1.03–2.13; $p = 0.0355$]) and normofractionated RT (adjusted OR 1.88 [95% CI 1.06–3.31; $p = 0.0298$]) were associated with increased odds of severe global fatigue. In addition, there was a significant association between normofractionated RT (adjusted OR 1.849 [95% CI 1.04–3.3; $p = 0.0354$]) and an increased likelihood of severe physical fatigue.

Conclusion: We found a significant association between internal mammary chain RT (versus No), normofractionated RT (versus hypofractionated RT) and increased likelihood of persistent severe global fatigue. Our data add to the current understanding of treatment-related factors affecting fatigue after BC and could lead to personalised interventions to improve the prevention and management of this disabling symptom.

1. Introduction

Female breast cancer (BC) is the most commonly diagnosed cancer worldwide [1]. Over the years, improvements in early detection have enabled a growing population to be diagnosed and treated at an early disease stage [2]. Nearly 90% will be cured and can expect a long-term disease-free survival [3]. In developed countries, it is estimated that 5 million women have had a history of BC [4]. The survivorship period represents a large part in their life. A better understanding of the long-term side effects of cancer treatments is necessary to prevent them and improve their management through targeted interventions.

Fatigue is one of the most common disabling symptoms experienced after BC treatment, significantly impacting quality of life with substantial adverse physical, psychosocial and socioeconomic consequences [5]. Approximately 30% of patients experience persistent fatigue 1 year after treatment completion [6–8]. Data on cancer survivors suggest that fatigue can persist up to 5 years after treatment [9] and in some cases even longer [10]. Nevertheless, this complex symptom remains underreported and poorly managed [11].

Fatigue related to BC has several dimensions and manifestations that can be physical, psychological or cognitive. Available data suggest that this multifactorial symptom strongly correlates to patient characteristics, demographical factors (such as marital status and level of income), psychosocial, cognitive and behavioural factors (such as depression, sleep disturbance, pretreatment fatigue, body mass index and inactivity), medical comorbidities, biological factors including inflammation, disease characteristics and antineoplastic therapies [5].

Previous studies have identified treatment-related factors associated with increased risk of developing severe and persistent fatigue [12].

Radiation therapy (RT) is a cornerstone of multimodal treatment for BC, which reduces the risk of local recurrence and prolongs overall survival (OS) [13,14]. Prior data indicate that RT can induce fatigue via a number of biological mechanisms, such as mitochondrial dysfunction, and enhanced immune response [15,16]. Furthermore, studies have shown that RT is associated with an increased prevalence of fatigue and levels of inflammatory markers [15,17] (such as interleukin-6, interleukin-10 and soluble tumour necrosis factor receptors), which might be influenced by recent changes in RT practice [18–21].

RT modalities are now increasingly personalised (including delivery techniques, volumes, doses and fractionation regimens), with great interindividual variability across patients, treating centres and countries. While an association between RT and fatigue after BC was previously suggested [15,22], large-scale data

analysing the impact of distinct RT modalities on fatigue are lacking.

We aimed to assess the impact of RT modalities on fatigue 1 year after treatment completion among patients with early-stage BC.

2. Materials and methods

2.1. Study design and patient selection

We used data from the CANcer TOxicity cohort (CANTO; NCT01993498), a multicentric nationwide prospective cohort of 10,150 patients with stages I–III BC diagnosed and recruited from June 2012 to February 2017 across 26 French centres. Details about the CANTO study procedures were previously published [23].

This analysis was performed in CANTO-RT, a subcohort of CANTO including 3875 patients who received RT in the ten top recruiting CANTO centres, with a minimum follow-up of 3 years, as described in Fig. 1. The final analytic cohort included 3295 patients. In previously published analyses from our group, factors associated with fatigue at year 1 were assessed, and a model for the prediction of severe fatigue was developed and validated [24]. In this study, we specifically focused on RT modalities and their association with fatigue at year 1 where there were high rates of responses to fatigue questionnaires and prevalence of severe fatigue.

Patients without fatigue data available at year 1 were not included (N = 502). To assess the potential bias introduced by the exclusion of patients with missing fatigue evaluation at year 1, their characteristics were compared with those of included patients. Patients missing evaluation tended to be younger, earned a lower income per month, were more frequently former or current smokers, had higher stage BC and received more frequently chemotherapy and less frequently endocrine therapy. They also had more frequently and more extensive local treatment including mastectomy, axillary dissection and nodal irradiation, including internal mammary chain (IMC) RT.

All CANTO-RT patients underwent breast/chest wall ± lymph node RT with curative intent. Among them, 3797 patients received unilateral RT. Individual full DICOM-RT files (simulation computed tomography, RT-structure, RT-dose, RT-plan) were collected, pseudo-anonymised, structured and analysed on the CANTO-RT/UNITRAD web platform using AQUILAB Share Place and Analytics Dose module.

We used data and outcome assessment collected at diagnosis (baseline) and at year 1 after treatment defined as completion of RT. Adjuvant endocrine and anti–human epidermal growth factor receptor 2 (HER2) therapies were allowed according to local guidelines. All patients provided written informed consent. The study protocol was approved by a central ethical committee.

2.2. Variables of interest

2.2.1. Outcomes of interest

The primary outcome was severe global fatigue at year 1, defined by the European Organization for Research

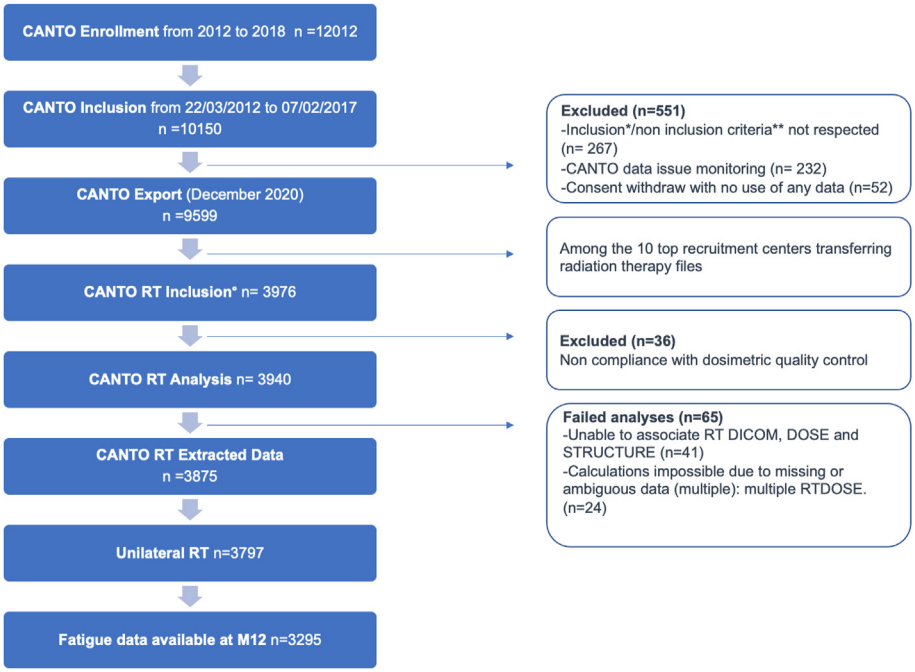


Fig. 1. Flowchart.

and Treatment of Cancer Quality of Life Questionnaire-C30 score ≥40/100 [25]. The secondary outcomes included severe physical, emotional and cognitive dimensions of fatigue using the Quality of Life Questionnaire-FA12 [25] defined as a binary variable (scores ≥40/100 defined severe fatigue). The severity threshold was defined as in Abrahams et al. [26] for global fatigue and fatigue dimensions, based on agreement analyses showing satisfactory concordance between global fatigue and distinct dimensions.

2.2.2. Independent variables

The following RT-related variables were used as independent variables: conformal three-dimensional RT versus intensity-modulated radiation therapy, normofractionated (50 Gy/25 fractions/5 weeks ± tumour bed boost of 16 Gy/8 fractions/1.5 week) versus hypofractionated RT mostly (75%) 40.05 Gy/15 fractions/3 weeks or 42.4 Gy/16 fractions/3.1 weeks ± tumour bed boost of 16 Gy/8 fractions/1.5 weeks), boost to tumour bed (Yes versus No), laterality (left versus right), Nodal RT no matter the node level (Yes versus No) and Nodal RT including at least the IMC (Yes versus No).

2.2.3. Covariates

We analysed baseline clinical features (age, body mass index [BMI], menopausal status, Charlson comorbidity index [27], marital status, education level, income, daily consumption of alcohol, tobacco use, physical activity, tumour stage and histological subtype), treatment (axillary management, type of breast surgery, receipt of chemotherapy, endocrine therapy, anti-HER2 therapy and RT) and symptoms (emotional distress, insomnia, pain and hot flashes). Emotional distress (anxiety and depression) was assessed by the Hospital Anxiety and Depression Scale [28].

2.3. Statistical analysis

Descriptive statistics were used to summarise cohort characteristics overall. Chi-squared tests and Wilcoxon rank-sum tests were used to compare the distribution of categorical and continuous variables by severe fatigue, respectively.

We then used multivariate logistic regression models to identify RT variables associated with the presence of severe fatigue at year 1 (separate models for global, physical, emotional and cognitive fatigue). Models were adjusted for the aforementioned baseline covariates.

Statistical analysis was performed using SAS statistical software version 9.4 (SAS Institute Inc.). Statistical significance was defined with a two-sided p value <0.05.

3. Results

3.1. Characteristics of overall study population

Among the 3295 patients included in the final cohort, 2056 were postmenopausal (63%), 2052 were never smokers (63%), 1729 received chemotherapy (52%) and 2693 endocrine therapy (82%). Patient characteristics are shown in Table 1.

Conformal three-dimensional RT was delivered in 3161 patients (96%) mostly with normofractionated (2 Gy/fraction) RT (n = 2332; 93%). The majority of patients (n = 2294; 70%) received a tumour bed boost. Nodal RT was delivered in 1095 patients (33%), including 666 (22%) with IMC RT.

3.2. RT and severe global fatigue

The prevalence of severe global fatigue in this cohort was 33.3% at year 1. Patients reporting severe fatigue tended to be younger, with higher BMI, current smokers, have lower income, present higher tumour stage, receive chemotherapy and report a higher depression score and more anxiety (data not shown).

Patients treated with normofractionated RT were younger (mean age 56.0 versus 68.0 years, $p < 0.0001$), tended to be premenopausaled, had fewer comorbidities, were more often smokers or former smokers and tended to have a higher level of education and higher tumour stage. They more frequently underwent mastectomy and/or axillary dissection and/or adjuvant chemotherapy and/or anti-HER2 treatment and/or boost and/or lymph node irradiation (Table 2.).

After correction for age, BMI, comorbidities, income, smoking behaviour, anxiety, depression, receipt of chemotherapy and endocrine therapy, there was a significant relationship between RT modalities and severe global fatigue. Specifically, IMC RT versus no IMC RT (adjusted odds ratio [OR] 1.48 [95% confidence interval [CI] 1.03–2.13; $p = 0.0355$]) and normofractionated versus hypofractionated RT (adjusted OR 1.88 [95% CI 1.06–3.31; $p = 0.0298$]) were associated with increased odds of persistent severe global fatigue. Other associations are displayed in Fig. 2. For the systemic treatment factors, there was also a significant relationship between receipt of chemotherapy and severe global fatigue (OR 1.37 [95% CI 1.084–1.733; $p = 0.0085$]), whereas no association has been found for receipt of endocrine therapy at year 1 (Supplementary Table 1).

3.3. RT and severe fatigue dimensions

Overall, 33%, 20.4% and 12.9% of patients reported severe physical, emotional and cognitive fatigue, respectively.

There was a significant association between normofractionated versus hypofractionated RT (adjusted OR

Table 1
Patient's clinical and treatment characteristics.

Characteristics	Breast cancer patients, *n* (%) or mean (range)
Clinical factors	
Age at enrolment	
Mean (range), years	57.0 (25.9–85.8)
Menopausal status	
Premenopausal	1205 (36.9)
Postmenopausal	2056 (63.1)
Missing	34
Charlson comorbidity score	
0	2522 (82.5)
≥1	535 (17.5)
Missing	238
Tobacco use behaviour	
Current smoker	534 (16.4)
Former smoker	664 (20.4)
Never smoker	2052 (63.2)
Missing	45
Alcohol consumption behaviour	
Less than daily	2792 (86.5)
Daily	437 (13.5)
Missing	66
Education	
Primary school	418 (13.3)
High school	1394 (44.5)
College or higher	1323 (42.2)
Missing	160
Income[a]	
<1500	412 (13.3)
≥1500 to <3000	1250 (40.4)
>3000	1435 (46.3)
Missing	198
Marital status	
Not partnered	691 (21.9)
Partnered	2470 (78.1)
Missing	134
AJCC stage	
Stage I	1678 (51.4)
Stage II	1293 (39.6)
Stage III	296 (9.0)
Missing	28
Molecular subtype	
HR+HER2+	323 (9.8)
HR+HER2−	2522 (76.8)
HR−HER2+	136 (4.2)
HR−HER2−	301 (9.2)
Missing	13
Treatment factors	
Type of breast surgery	
Lumpectomy	2695 (81.8)
Mastectomy	600 (18.2)
Type of lymph node surgery	
Sentinel node biopsy	2406 (73)
Axillary clearance	889 (27)
Chemotherapy	
No chemotherapy	1566 (47.5)
Chemotherapy	1729 (52.5)
Endocrine therapy	
No	602 (18.3)
Yes	2693 (81.7)
Herceptin treatment	
No or not applicable	2887 (87.6)
Yes	408 (12.4)
Radiation therapy modalities	
Radiation therapy	
Right side	1598 (51.5)
Left side	1697 (48.5)
Patients with tumour bed boost	
No or not applicable	1001 (30.4)
Yes	2294 (69.6)
Lymph node levels treated	
None	2200 (66.8)
Yes	1095 (33.2)
IMC RT	*666*
No IMC RT	*2629*
Irradiation techniques	
3D	3161 (95.9)
IMRT	134 (4.1)
Fractionation regimens	
Normofractionation[c]	2332 (92.8)
Hypofractionation[b]	181 (7.2)
40.05 Gy/15 fractions/3 weeks or 42.4 Gy/16 fractions/3.1 weeks	*135*
More hypofractionated regimen (>3 Gy/fraction)	*46*
Unspecified fractionation – missing[b]	782
Symptoms	
Anxiety	
Normal	1289 (40.8)
Borderline	818 (25.9)
Case	1050 (33.3)
Missing	138
Depression	
Normal	2620 (82.9)
Borderline	328 (10.4)
Case	211 (6.7)
Missing	136
Hot flashes	
No	2328 (74.2)
Yes	811 (25.8)
Missing	156

BMI, body mass index; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IMC, internal mammary chain; IMRT, intensity-modulated radiation therapy.
Anxiety and depression scored according to the Hospital Anxiety and Depression Scale: normal (score 0–7), borderline (8–10), case (11–21).
[a] Euro per month.
[b] 40.05 Gy/15 fractions/3 weeks or 42.4 Gy/16 fractions/3.1 weeks ± tumour bed boost of 16 Gy/8 fractions/1.5 week or more hypofractionated regimen (>3 Gy/fraction).
[c] 50 Gy/25 fractions/5 weeks ± followed by a tumour bed boost of 16 Gy/8 fractions/1.5 week.

1.849 [95% CI 1.04–3.3; $p = 0.0354$]) and an increased likelihood of persistent severe physical fatigue reported.

None of the investigated RT modalities seemed to be associated with emotional and cognitive fatigue dimensions (Fig. 3A–C for severe physical, emotional and cognitive fatigue, respectively).

4. Discussion

Most patients will experience fatigue during the treatment of BC and particularly during RT [16]. Severe fatigue can persist for years after treatment completion [9].

Table 2
Patient's clinical and treatment characteristics by fractionation.

Characteristics	Breast cancer patients, n (%) or mean (range)		
	Hypofractionation[a]	Normofractionation[b]	*p* value
Clinical factors			
Age at enrolment			<0.0001
Mean (range), years	68.0(29.1–85.2)	56.0(25.9–85.9)	
Menopausal status			<0.0001
Premenopausal	7 (0.3)	902(36.3)	
Postmenopausal	174 (7)	1403 (56.4)	
Missing	809		
Charlson comorbidity score			0.00214
0	112 (4.9)	1714 (74.8)	
≥1	43 (1.9)	422 (18.4)	
Missing	1004		
Tobacco use behaviour			0.0021
Current smoker	15 (0.6)	397 (16)	
Former smoker	36 (1.5)	488 (19,6)	
Never smoker	129 (5.2)	1419 (57.1)	
Missing	811		
Alcohol consumption behaviour			0.0016
Less than daily	142 (5.8)	2016 (81.6)	
Daily	37 (1.5)	274(11.1)	
Missing	826		
Education			0.0577
Primary school	36 (1.5)	324 (13.6)	
High school	74 (3.1)	1067 (44.8)	
College or higher	55 (2.3)	827 (34.7)	
Missing	912		
Income[a]			0.2628
<1500	24 (1)	322 (13.6)	
≥1500 to <3000	81 (3.4)	937 (39.7)	
>3000	61 (2.6)	939 (39.7)	
Missing	931		
Marital status			0.1452
Not partnered	44 (1.8)	476 (19.8)	
Partnered	124 (5.2)	1760 (73.2)	
Missing	891		
AJCC stage			<0.0001
Stage I	144 (5.9)	1160 (46.6)	
Stage II	28 (1.1)	951 (38.2)	
Stage III	6 (0.2)	200 (8)	
Missing	803		
Molecular subtype			<0.0001
HR+HER2+	4 (0.2)	250 (10)	
HR+HER2−	163 (6.5)	1744 (69.8)	
HR−HER2+	0 (0)	95 (3.8)	
HR−HER2−	12 (0.5)	232 (9.3)	
Missing	795		
Treatment factors			
Type of breast surgery			<0.0001
Lumpectomy	176 (7)	2022 (80.5)	
Mastectomy	5 (0.2)	310 (12.3)	
Missing	782		
Type of lymph node surgery			<0.0001
Sentinel node biopsy	167(6.7)	1717 (68.3)	
Axillary clearance	14 (0.6)	615 (24.5)	
Missing	782		
Chemotherapy			<0.0001
No chemotherapy	152 (6)	1060 (42.2)	
Chemotherapy	29 (1.2)	1272 (50.6)	
Missing	782		
Endocrine therapy			0.3028
No	28 (1.1)	431 (17.2)	
Yes	153 (6.1)	1901 (75.6)	
Missing	782		

Table 2 (*continued*)

Characteristics	Breast cancer patients, n (%) or mean (range)		
	Hypofractionation[a]	Normofractionation[b]	*p* value
Herceptin treatment			<0.0001
No or not applicable	176 (7)	2031 (80.8)	
Yes	5 (0.2)	301 (12)	
Missing	782		

[a] 40.05 Gy/15 fractions/3 weeks or 42.4 Gy/16 fractions/3.1 weeks +/− tumor bed boost of 16 Gy/8 fractions/1.5 week or more hypofractionated regimen (>3 Gy/fraction).
[b] 50 Gy/25 fractions/5 weeks +/− followed by a tumor bed boost of 16 Gy/8 fractions/1.5 week.

Consistent with previous data, we have shown in our study that more than one-third of patients will experience persistent severe fatigue 1 year after treatment.

In contrast to most studies, which were mainly retrospective, cross-sectional and focused on the impact of RT on fatigue during or immediately after treatment, we evaluated the impact of RT modalities on fatigue at year 1 in BC survivors.

Our findings are state of the art as no previous study using large-scale data and a longitudinal design with a follow-up from diagnosis to the survivorship period has shown an impact of RT modalities on fatigue.

CANTO-RT is one of the largest early BC prospective cohorts worldwide with full individual DICOM-RT data available. Moreover, this is the first study that has investigated specifically the associations between RT modalities and different dimensions of persistent fatigue 1 year after treatment completion. Another strength of the study is the use of a well-established methodology for fatigue assessment and the use of a model previously validated and published [24]. Limitations should not be ignored. CANTO is a longitudinal study but non-randomised cohort with inherent bias such as heterogeneity between groups, and reduction of patient retention over the follow-up is inevitable and expected. The cohort lost the fatigue data of 502 patients (13%) at year 1. When comparing the patients who are included and excluded at year 1, the characteristics of patients who were excluded were very similar to those who experienced persistent fatigue.

Our findings show that IMC RT is associated with increased odds of persistent severe global fatigue at year 1. This association could be correlated with cardiac exposure to RT as IMC RT increases significantly heart dose [18] and the prevalence of fatigue in patients with cardiac heart failure is high [29]. It will be interesting to assess the impact of protons on fatigue in ongoing randomised trials for BC patients with high risk of cardiac toxicity such as UK PARABLE (NIHR131120).

Previous studies have shown that IMC RT increases OS, but this increase is likely to be small and probably limited to a specific subgroup of patients [19]. However, despite four major randomised trials assessing IMC RT, there is still a debate regarding the criteria to identify patients benefiting from IMC RT [20,30,31]. The risk of developing persistent severe fatigue at 1 year might be considered in the balance by the physician and the

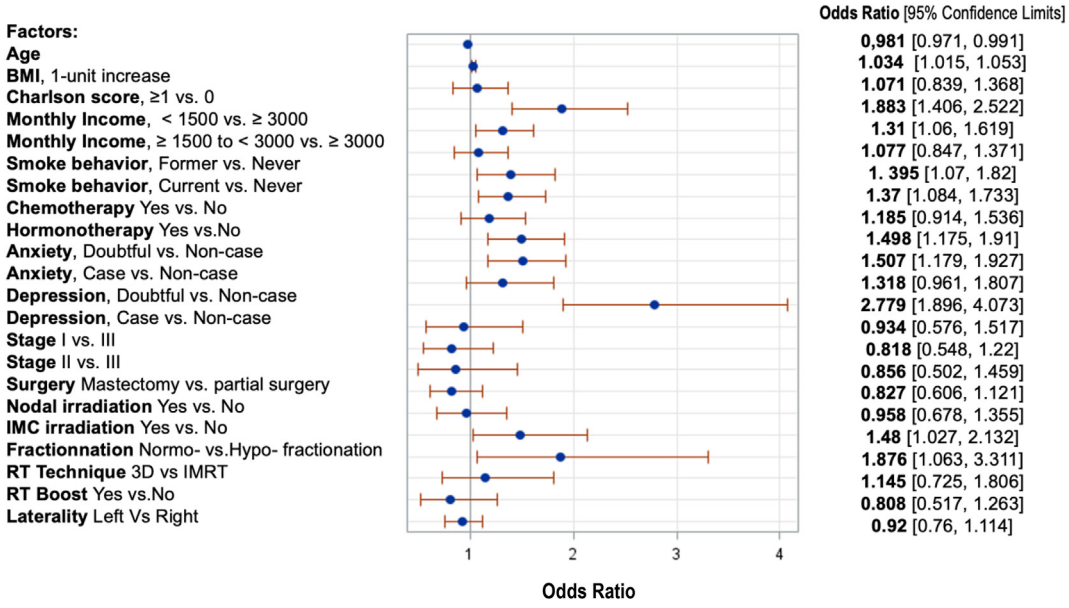
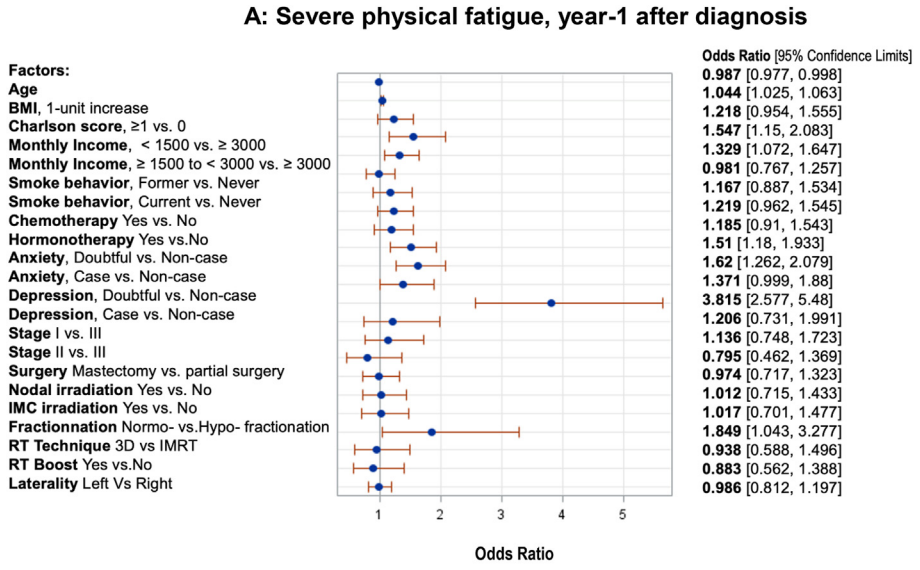
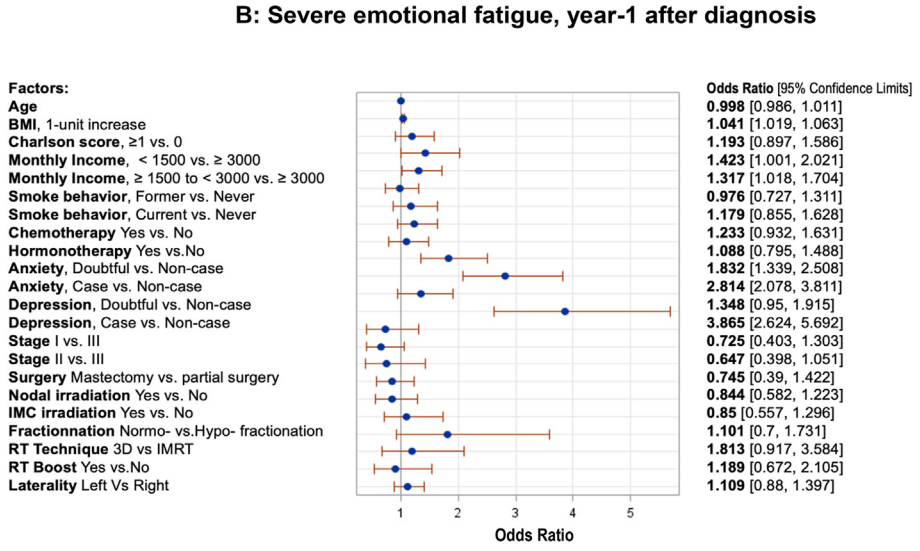


Fig. 2. Severe global fatigue, year 1 after diagnosis.





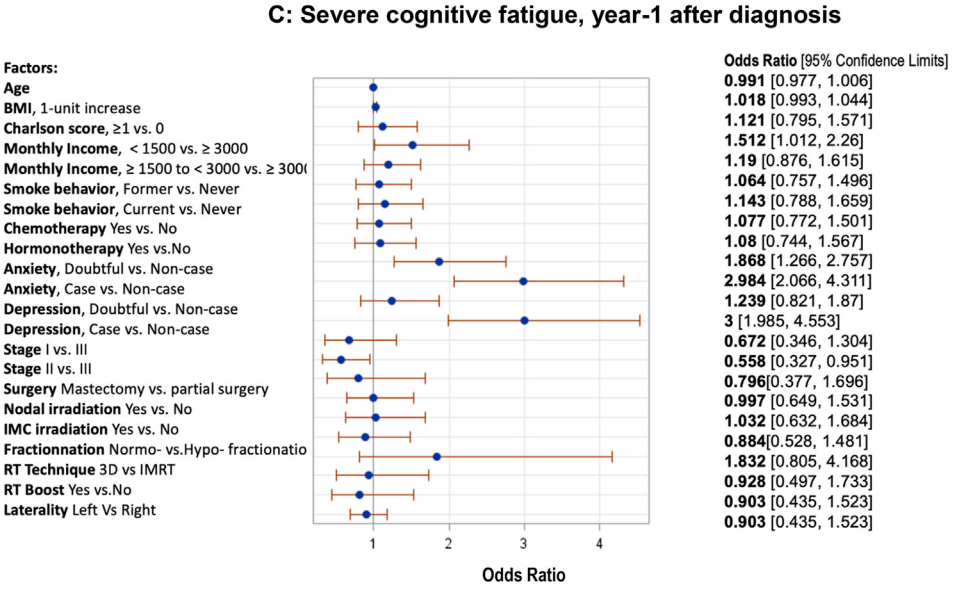


Fig. 3. (A) Severe physical fatigue, year 1 after diagnosis. (B) Severe emotional fatigue, year 1 after diagnosis. (C) Severe cognitive fatigue, year 1 after diagnosis.

patient during the shared decision-making process when IMC RT is discussed. Specially for high-risk patients, the benefit of IMC RT could outweigh the risk of fatigue.

Moreover, increased RT field size and thoracic localisation of the IMC could induce biological mechanisms related to fatigue. It is recognised that radiation-induced lymphopenia risk is correlated with field size, circulating blood volume, dose per fraction and fraction number [32]. The IMC RT may affect immunological mechanisms that remain to be explored, causing severe and persistent fatigue.

Randomised studies have established that hypofractionated and accelerated RT is as effective as normofractionated RT on OS and might result in lower rates of late toxicity for whole breast RT [33].

Hypofractionated regimens tend to use a lower biologically effective dose, which may result in less biological effects on the surrounding normal tissues. Even if there is no α/β validated for fatigue, the higher biologically effective dose of normofractionated versus hypofractionated RT may explain the increased fatigue observed with normofractionated RT in our study. Despite an adjustment for the aforementioned baseline covariates, a selection bias cannot be excluded because normofractionated RT was largely predominant in our series and commonly used in younger patients with higher disease burden, who therefore received more extended local and systemic adjuvant treatments. Some of these factors such as younger age were previously associated with higher likelihood of severe fatigue at year 2 [24]. We acknowledge that treatment between 2012 and 2017 is somewhat historical with majority of patients receiving conformal normofractionated RT. Most patients would now be expected to receive hypofractionated RT with more frequent intensity-modulated radiation therapy. Recently, a randomised multicentric trial has shown that an ultra-hypofractionated regimen delivering 26 Gy in five fractions over 1 week is non-inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control and is safe in terms of normal tissue effects with a 5-year follow-up [34]. That type of regimen is becoming a standard of care for non-nodal breast or chest wall RT [21].

In the present analysis, we found an association between chemotherapy and severe fatigue at year 1 (OR 1.37 [1.084–1.733]; $p = 0.0085$), whereas endocrine therapy was not associated with this outcome. These associations are consistent with those observed in previous [24] analyses where a potential impact of chemotherapy on fatigue was found closer to chemotherapy completion, whereas an association with endocrine therapy only emerged later on (i.e. at year 3).

Currently, there is no 'gold standard' treatment for cancer-related fatigue. Randomised trials conducted with patients during and after treatment showed beneficial effects of physical exercise on fatigue after treatment completion [35]. Psychological interventions can have a positive impact as well on fatigue by providing patients with cognitive and behavioural strategies [36]. Other approaches such as mind-body intervention including acupuncture have shown beneficial effects [37]. Presently, there is no validated pharmacological intervention for patients with persistent fatigue after BC treatment, but studies have shown a decrease in fatigue after administration of anti-cytokinin agent [38,39].

In conclusion, more than one-third of early BC patients with a multimodal treatment including RT in the CANTO-RT cohort reported severe fatigue 1 year after treatment. We found a significant association between IMC RT, normofractionated RT and increased likelihood of severe global fatigue. Moreover, normofractionated was associated with physical fatigue, whereas hypofractionated RT was neither associated with severe global fatigue nor to any fatigue dimension. Our data add to the current understanding of treatment-related factors affecting fatigue after BC treatment and could lead to personalised interventions to improve the prevention and management of this disabling symptom.

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Authors' contributions

Y.G., A.D.M., I.V.L. and S.R. contributed to conceptualisation; investigation; methodology; and writing, reviewing and editing the article. A.J., S.E., A.D.M., T.S., Y.G. and S.R. contributed to data curation, resources and software. A.D.M. contributed to formal analysis. A.J. and S.E. contributed to project administration. T.S., A.J., S.E., Y.K., K.P., P.G., C.C.-B., J.B., O.F.B., D.P., S.R., C.B., J.G., A.B., F.P. and G.A. contributed to investigation and reviewing and editing the article. S.R., I.V.L. and A.D.M. contributed to supervision and validation.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as

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Appendix A. Supplementary data

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