

1 **Supplementary material**

2

3 **Pre-treatment risk factors for late fatigue and fatigue trajectories following radiotherapy**
4 **for breast cancer**

5 Juan C. Rosas, Miguel E. Aguado-Barrera, David Azria, Erik Briers, Rebecca Elliott, Marie-Pierre Farcy-
6 Jacquet, Alexandra Giraldo, Sara Gutiérrez-Enríquez, Tiziana Rancati, Tim Rattay, Victoria Reyes, Barry
7 Rosenstein, Dirk De Ruyscher, Elena Sperk, Hilary Stobart, Christopher Talbot, Ana Vega, Begoña
8 Taboada-Valladares, Liv Veldeman, Tim Ward, Adam Webb, Catharine West, Jenny Chang-Claude, Petra
9 Seibold¹ on behalf of the REQUITE Consortium

10

11 **Table of Contents**

12 **Table S1.** Comparison between groups with and without long-term data2

13 **Table S2.** Results from linear mixed models for mean fatigue differences5

14

15 **Results from logistic regression models on the five MFI-20 fatigue dimensions**

16 **Table S3.** Logistic regression model on General fatigue6

17 **Table S4.** Logistic regression model on Physical fatigue7

18 **Table S5.** Logistic regression model on Mental fatigue8

19 **Table S6.** Logistic regression model on Reduced motivation9

20 **Table S7.** Logistic regression model on Reduced activity10

21 **Figure S1.** Summary plot with model estimators for LCGA models11

22

23

24

25

26

27

1 **Table S1.** Overall baseline patient characteristics in breast cancer patients and comparison between
 2 patients with and without MFI-20 data at two years.

3

	Patients with MFI-20 data at two years (N=1069)	Patients without MFI-20 data at two years (N=374)	Overall (N=1443)	P-value
Age (years)				
Mean (SD)	57.9 (10.9)	58.9 (11.4)	58.2 (11.0)	0.145
Median [Min, Max]	58.0 [23.0, 87.0]	58.0 [31.0, 89.0]	58.0 [23.0, 89.0]	
<50	253 (23.7%)	89 (23.8%)	342 (23.7%)	0.569
50-59	342 (32.0%)	107 (28.6%)	449 (31.1%)	
60-69	315 (29.5%)	114 (30.5%)	429 (29.7%)	
>=70	159 (14.9%)	64 (17.1%)	223 (15.5%)	
Living status				
Living alone	202 (18.9%)	70 (18.7%)	272 (18.8%)	0.736
Not living alone	657 (61.5%)	213 (57.0%)	870 (60.3%)	
Missing	210 (19.6%)	91 (24.3%)	301 (20.9%)	
Educational level				
Low	171 (16.0%)	62 (16.6%)	233 (16.1%)	0.185
Medium	424 (39.7%)	112 (29.9%)	536 (37.1%)	
High	309 (28.9%)	99 (26.5%)	408 (28.3%)	
Missing	165 (15.4%)	101 (27.0%)	266 (18.4%)	
BMI (kg/m²)				
Mean (SD)	26.5 (5.57)	27.4 (6.77)	26.8 (5.91)	0.0343
Median [Min, Max]	25.5 [16.9, 61.8]	26.3 [13.1, 65.4]	25.6 [13.1, 65.4]	
categories (kg/m²)				
<25	506 (47.3%)	157 (42.0%)	663 (45.9%)	0.111
25-29	308 (28.8%)	109 (29.1%)	417 (28.9%)	
>=30	251 (23.5%)	106 (28.3%)	357 (24.7%)	
Missing	4 (0.4%)	2 (0.5%)	6 (0.4%)	
Smoking status				
Current	192 (18.0%)	73 (19.5%)	265 (18.4%)	0.554
Never/former	877 (82.0%)	301 (80.5%)	1178 (81.6%)	
Depression				
No	953 (89.1%)	321 (85.8%)	1274 (88.3%)	0.104
Yes	116 (10.9%)	53 (14.2%)	169 (11.7%)	

	Patients with MFI-20 data at two years (N=1069)	Patients without MFI-20 data at two years (N=374)	Overall (N=1443)	P-value
Time spent sitting (minutes per day)				
Mean (SD)	344 (197)	345 (217)	345 (203)	0.962
Median [Min, Max]	300 [0, 1200]	285 [0, 1380]	300 [0, 1380]	
Missing	239 (22.4%)	74 (19.8%)	313 (21.7%)	
Global Health Status / QoL (EORTC QLQ- C30)				
Mean (SD)	68.6 (20.5)	68.9 (19.8)	68.7 (20.3)	0.751
Median [Min, Max]	66.7 [0, 100]	66.7 [0, 100]	66.7 [0, 100]	
Missing	6 (0.6%)	1 (0.3%)	7 (0.5%)	
Pain (EORTC QLQ- C30)				
Mean (SD)	20.6 (23.6)	20.9 (24.9)	20.6 (24.0)	0.837
Median [Min, Max]	16.7 [0, 100]	16.7 [0, 100]	16.7 [0, 100]	
Missing	5 (0.5%)	0 (0%)	5 (0.3%)	
Insomnia (EORTC QLQ-C30)				
Mean (SD)	33.3 (30.9)	34.1 (33.9)	33.5 (31.7)	0.675
Median [Min, Max]	33.3 [0, 100]	33.3 [0, 100]	33.3 [0, 100]	
Missing	17 (1.6%)	2 (0.5%)	19 (1.3%)	
Radiotherapy boost				
No	382 (35.7%)	168 (44.9%)	550 (38.1%)	0.00203
Yes	687 (64.3%)	206 (55.1%)	893 (61.9%)	
Fractionation scheme				
Hypofractionation (> 2 Gy)	350 (32.7%)	145 (38.8%)	495 (34.3%)	0.0403
Conventional fractionation (\leq 2 Gy)	719 (67.3%)	229 (61.2%)	948 (65.7%)	
IMRT				
No	704 (65.9%)	232 (62.0%)	936 (64.9%)	0.182
Yes	362 (33.9%)	142 (38.0%)	504 (34.9%)	
Missing	3 (0.3%)	0 (0%)	3 (0.2%)	
Histologic type				
in situ	128 (12.0%)	41 (11.0%)	169 (11.7%)	0.771
Invasive	934 (87.4%)	322 (86.1%)	1256 (87.0%)	

	Patients with MFI-20 data at two years (N=1069)	Patients without MFI-20 data at two years (N=374)	Overall (N=1443)	P-value
Missing	7 (0.7%)	11 (2.9%)	18 (1.2%)	
Surgery type				
Segmentectomy/Quadrantectomy	801 (74.9%)	246 (65.8%)	1047 (72.6%)	0.00761
Wide local excision	260 (24.3%)	115 (30.7%)	375 (26.0%)	
Missing	8 (0.7%)	13 (3.5%)	21 (1.5%)	
Endocrine therapy				
No	239 (22.4%)	81 (21.7%)	320 (22.2%)	1
Yes	830 (77.6%)	282 (75.4%)	1112 (77.1%)	
Missing	0 (0%)	11 (2.9%)	11 (0.8%)	
Chemotherapy				
No	715 (66.9%)	272 (72.7%)	987 (68.4%)	0.00644
Yes	344 (32.2%)	89 (23.8%)	433 (30.0%)	
Missing	10 (0.9%)	13 (3.5%)	23 (1.6%)	
Pathological tumor stage^a				
Tis-T1	858 (80.3%)	294 (78.6%)	1152 (79.8%)	0.851
T2-T4	180 (16.8%)	59 (15.8%)	239 (16.6%)	
Missing	31 (2.9%)	21 (5.6%)	52 (3.6%)	
General fatigue at baseline (continuous)				
Mean (SD)	11.0 (4.34)	11.5 (4.29)	11.1 (4.33)	0.0821
Median [Min, Max]	11.0 [4.00, 20.0]	12.0 [4.00, 20.0]	11.0 [4.00, 20.0]	
Missing	23 (2.2%)	5 (1.3%)	28 (1.9%)	

1 ^a Data on pathological tumor stage was replaced by clinical tumor stage in case of missing values and available clinical data.

2 Abbreviations: BMI: Body Mass Index; IMRT: Intensity-modulated radiation therapy

1 **Table S2.** Results from linear mixed models for mean fatigue differences between T1 (prior to
 2 radiotherapy (RT)), T2 (end of RT) and T4 (24 months after RT) for all MFI-20 dimensions grouped by
 3 chemotherapy (yes vs. no) status at baseline

	Mean MFI-20 scores			Pair-wise p-values		
	t1	t2	t4	t1 vs. t2	t1 vs. t4	t2 vs. T4
Without chemotherapy						
MFI-20 dimensions						
general fatigue	10.5	12.1	10.7	<0.0001*	0.05	<0.0001*
physical fatigue	10.0	10.9	9.6	<0.0001*	0.01	<0.0001*
mental fatigue	8.3	8.8	8.3	<0.0001*	0.66	0.001*
reduced motivation	8.7	9.5	8.6	<0.0001*	0.28	<0.0001*
reduced activity	9.5	10.4	8.9	<0.0001*	0.0001*	<0.0001*
With chemotherapy						
MFI-20 dimensions						
general fatigue	12.6	12.8	11.1	0.38	<0.0001*	<0.0001*
physical fatigue	12.0	11.6	9.9	0.06	<0.0001*	<0.0001*
mental fatigue	9.3	9.5	8.9	0.35	0.06	0.008
reduced motivation	9.0	9.1	8.0	0.6	<0.0001*	<0.0001*
reduced activity	10.9	10.8	8.8	0.8	<0.0001*	<0.0001*

* Significant p-values at Bonferroni corrected significance threshold of < 0.0085

4

5

1 **Table S3.** Logistic regression models on general fatigue (score >12 vs ≤12) at 24 months in breast cancer
 2 patients, stratified by chemotherapy status

Patient characteristics	without chemotherapy (n=646)			with chemotherapy (n=320)		
	OR	95% CI	p-value	OR	95% CI	p-value
General fatigue at baseline (yes vs. no)	3.81	2.52, 5.78	<0.001	3.89	2.18, 7.08	<0.001
Age (continuous, 5-unit increment)	-	-	-	-	-	-
BMI (continuous)	-	-	-	1.05	1.00, 1.11	0.035
Depression	2.24	1.27, 3.96	0.005	-	-	-
Global Health Status (QLQ-C30) (10-unit increment)	-	-	-	0.75	0.63, 0.87	<0.001
Pain (QLQ-C30) (10-unit increment)	1.12	1.02, 1.23	0.021	-	-	-
Insomnia (QLQ-C30) (10-unit increment)	1.09	1.02, 1.16	0.010	1.15	1.06, 1.26	0.002
Dyspnea (QLQ-C30) (10-unit increment)	1.14	1.03, 1.27	0.009	-	-	-
Breast symptoms (BR23) (10-unit increment)	-	-	-	1.13	0.95, 1.35	0.180
Radiotherapy boost (yes vs. no)	-	-	-	0.35	0.16, 0.73	0.005

3
 4
 5
 6
 7
 8
 9
 10
 11
 12
 13
 14
 15
 16
 17
 18
 19
 20

1 **Table S4.** Logistic regression models on physical fatigue (score >12 vs ≤12) at 24 months in breast cancer
 2 patients stratified by chemotherapy status

Patient characteristics	without chemotherapy (n=627)			with chemotherapy (n=325)		
	OR	95% CI	p-value	OR	95% CI	p-value
Physical fatigue at baseline (yes vs. no)	3.40	2.14, 5.40	<0.001	2.85	1.59, 5.21	<0.001
Age (continuous, 5-unit increment)	1.15	1.04, 1.28	0.008	-	-	-
BMI (continuous)	1.05	1.01, 1.09	0.022	1.08	1.03, 1.13	0.001
Depression	1.93	1.07, 3.46	0.029	-	-	-
Alcohol consumption	1.86	0.93, 3.62	0.078	-	-	-
Global Health Status (QLQ-C30) (10-unit increment)	-	-	-	-	-	-
Pain (QLQ-C30) (10-unit increment)	1.19	1.07, 1.33	0.002	-	-	-
Insomnia (QLQ-C30) (10-unit increment)	1.08	1.01, 1.16	0.024	1.16	1.06, 1.28	0.001
Dyspnea (QLQ-C30) (10-unit increment)	1.11	1.00, 1.22	0.051	1.12	1.01, 1.24	0.032
Breast symptoms (BR23) (10-unit increment)	0.88	0.77, 1.01	0.077	1.19	1.00, 1.43	0.050
Endocrine therapy (yes vs. no)	-	-	-	1.85	0.88, 4.15	0.108
Fractionation (hypofractionation vs. standard)	-	-	-	0.46	0.24, 0.87	0.018

3

4

1 **Table S5.** Logistic regression models on mental fatigue (score >12 vs ≤12) at 24 months in breast cancer
 2 patients, stratified by chemotherapy status

Patient characteristics	without chemotherapy (n=631)			with chemotherapy (n=324)		
	OR	95% CI	p-value	OR	95% CI	p-value
Mental fatigue at baseline (yes vs. no)	3.68	2.18, 6.18	<0.001	5.43	2.94, 10.2	<0.001
Age (continuous, 5-unit increment)	0.93	0.83, 1.05	0.244	0.82	0.70, 0.96	0.011
Depression	1.98	1.06, 3.59	0.032	-	-	-
Alcohol consumption	1.83	0.85, 3.76	0.118	-	-	-
Global Health Status (QLQ-C30) (10-unit increment)	0.86	0.76, 0.96	0.008	-	-	-
Pain (QLQ-C30) (10-unit increment)	-	-	-	1.13	1.01, 1.27	0.033
Insomnia (QLQ-C30) (10-unit increment)	1.09	1.02, 1.17	0.016	-	-	-
RT boost (yes vs. no)	1.35	0.85, 2.17	0.203	-	-	-

3
 4
 5
 6
 7
 8
 9
 10
 11
 12
 13
 14
 15
 16
 17
 18
 19
 20
 21
 22
 23
 24
 25

1 **Table S6.** Logistic regression models on reduced motivation (score >12 vs ≤12) at 24 months in breast
 2 cancer patients, stratified by chemotherapy status

Patient characteristics	without chemotherapy (n=660)			with chemotherapy (n=322)		
	OR	95% CI	p-value	OR	95% CI	p-value
Reduced motivation at baseline (yes vs. no)	4.72	2.76, 8.10	<0.001	3.64	1.70, 7.63	0.001
Age (continuous, 5-unit increment)	1.17	1.05, 1.32	0.005	1.08	0.91, 1.29	0.376
Depression (yes vs. no)	-	-	-	2.41	0.92, 5.82	0.073
Global Health Status (QLQ-C30) (10-unit increment)	0.86	0.76, 0.97	0.018	-	-	-
Dyspnea (QLQ-C30) (10-unit increment)	1.10	0.99, 1.21	0.082	-	-	-
Type of surgery (segmentectomy vs. wide local excision)	-	-	-	1.79	0.73, 4.05	0.192
Endocrine therapy (yes vs. no)	2.27	1.26, 4.34	0.006	-	-	-

3

4

1 **Table S7.** Logistic regression models on reduced activity (score >12 vs ≤12) at 24 months in breast cancer
 2 patients, stratified by chemotherapy status

Patient characteristics	without chemotherapy (n=658)			with chemotherapy (n=323)		
	OR	95% CI	p-value	OR	95% CI	p-value
Reduced activity at baseline (yes vs. no)	3.49	2.17, 5.62	<0.001	2.46	1.20, 5.06	0.014
Age (continuous, 5-unit increment)	1.15	1.04, 1.29	0.009	1.05	0.89, 1.23	0.556
BMI (continuous)	-	-	-	1.09	1.03, 1.16	0.002
Depression	2.49	1.36, 4.51	0.003	-	-	-
Global Health Status (QLQ-C30) (10-unit increment)	0.79	0.71, 0.89	<0.001	0.80	0.66, 0.97	0.024
Pain (QLQ-C30) (10-unit increment)	-	-	-	1.09	0.95, 1.25	0.230
Insomnia (QLQ-C30) (10-unit increment)	-	-	-	1.13	1.02, 1.26	0.019
Dyspnea (QLQ-C30) (10-unit increment)	1.27	1.15, 1.41	<0.001	0.94	0.83, 1.06	0.289
IMRT (yes vs. no)	0.62	0.37, 0.99	0.046	-	-	-

3

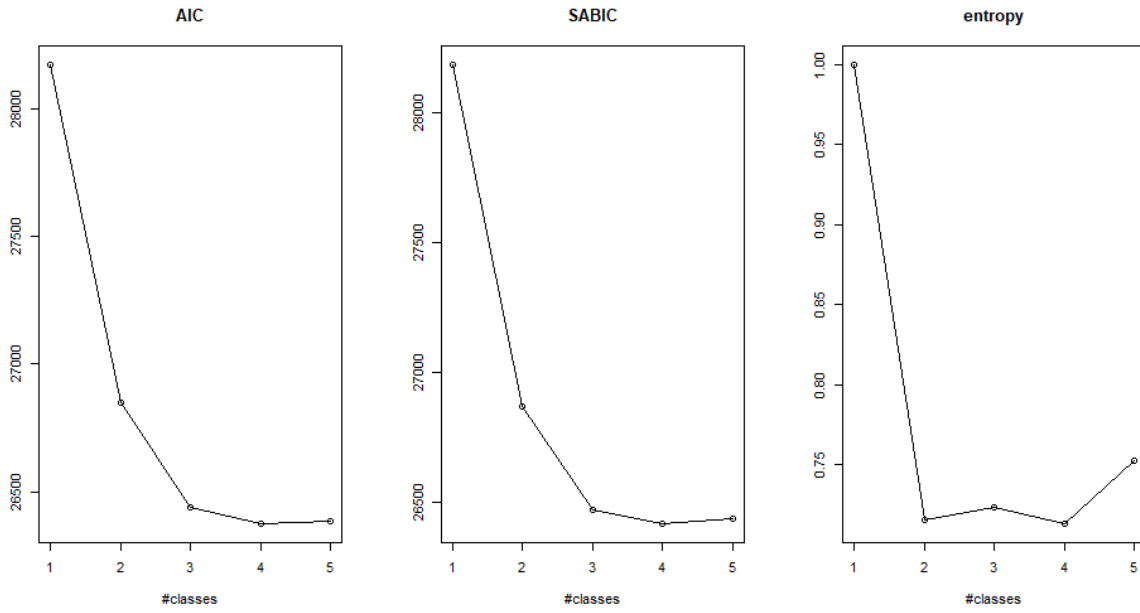


Figure S1. Summary plot with model estimators for LCGA models ranging from 1-5 latent classes
Abbreviations: AIC Akaike information criterion, SABIC sample size adjusted Bayesian information criteria