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Cancer Survivorship Fatigue: Characteristics, Multimodal Fatigue Interventions and Time Course of 108 Cancer Fatigue Clinic patients

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Background
Fatigue is the leading symptom of cancer survivors *[1]* with a substantial risk of disability. Cancer-related fatigue (CRF) is an experience of a subjective, persistent, feeling of tiredness, weakness, or lack of energy, which is not proportional to recent physical activity (as normal human experience) and is not alleviated through sleep or rest (as normal human experience). Cancer survivors suffering from CRF are therefore very often confronted with lack-of-understanding from non-cancer experienced people, which contributes to distress and also financial and vocational injustices. Phenomenologically CRF is characterized by physical (muscular), emotional, and cognitive components of fatigue, in individually variable degree and combination. CRF can have a major impact on patients' functioning and QoL. The **evidence** *[2,3,4]* for full multimodal intervention is still scarce since such complex trials are missing. The most effective CRF interventions are physical exercise and psychological interventions, there is increasing data on Mind-Body interventions, nutrition and sleep.

Recommendations for current screening, diagnosis and management of CRF

Patients shall be ***screened*** in routine care by simple assessment tools for fatigue (e.g., ESAS *[5]*), then ***assessed*** for impact of fatigue (e.g., Brief Fatigue Inventory *[6]*) and of fatigue domains (e.g., Single-Item-Fatigue *[7]*), and finally a list of possible reversible causes for fatigue shall be checked and treated (e.g., dehydration, hypercalcemia, hypothyroidism, anemia, anxiety/ depression {HADS *[8]*, BAI *[9]*, BDI *[10]*}, PTBS *[11]*, social factors {Distress Thermometer *[12]*}). Then a ***diagnosis*** of cancer-related fatigue (CRF) applies the DICRFS (Diagnostic Interview for Cancer Related Fatigue *[13]*), physical function test (e.g. Five-Times-Sit-To-Stand) *[14]*) and a neuropsychological examination *[15],* amended by patients' perception of self-management abilities *[16]* incl. coherence *[17]* and disability *[18]* .

Management of CRF shall be multimodal (Multi-Modal-Fatigue-Intervention: **7 typical MMFIs**) and include (a) physical exercise (endurance- and strength training), (b) nutrition with protein-rich diet & anti-inflammatory diet, (c) psychological and creative therapies to cope with disability, trauma, and (unconscious) emotions, (d) physical therapies (e.g., massage, acupressure), (e) Mind-Body interventions (e.g., yoga, mindfulness meditation, body scan, PMR, conscious breathing), (f) energy conservation and self-management enhancing psychoeducative and cognitive-behavioral interventions, (g) social work support and insurance advice, and (h) consider pharmacological treatment in few indications *[19]*.

Methods
The Cancer Fatigue Clinic applies an outpatient diagnostic workup (anticancer treatment history, ESAS *[5]*, *S*ingle-*I*tem-*F*atigue *[7]*, BFI *[6]*, DICRFS *[13]*, *D*istress-*T* *[12]* , WHODAS *[18]*, HADS *[8]*, BAI *[9]*, BDI *[10]*, *S*elf-*E*fficacy-*E*xpectation *[16]*, *C*oherence *[17]*, *S*creening-*PTBS* *[11]* , *F*ive-*T*ime-*S*it-*T*o-*S*tand *[14]*; Cofactors incl. Labs; *N*euro*PS*ychological Examination *[15]*), advice on MMFI *[19]* (number of MMFI-Elements), social aspects (living, financial and vocational situation, and insurance-medicine aspects.

Protocol-based (EKOS 2024-02085) data extracted from anonymized medical letters was analyzed (descriptive, Pearson, Anova, paired T-Test [SPSS]).

Cancer Fatigue Clinic *Cancer Fatigue Clinic*
(Locations: Oncology Schaffhausen, Oncology KS Münsterlingen, Sargans)
Special consultation hours for people severely affected by survivorship fatigue
Listening and ***hearing***, building ***trust***
Diagnostics (medical history, examination, assessments, co-factors, referrals)
Counselling (including psychoeducation) and multimodal («7 pillars») **treatment**
Understanding and acceptance Energy reserves, perception Energy investment
Recognising, reducing/eliminating Energy drainers, promoting Energy sources
Changing habits, '*here and now*', "*for what*", '*who am I/who will I become*'
Medicines/drugs (mainly Co-factors), prescriptions & referrals to therapists
Coordination of therapists, detailed reports
Possible cost approval for ***inpatient oncological rehabilitation***
Review ***insurance law issues*** (especially IV, daily sickness allowance)
Duration of consultation: 75–120 minutes (possibly with breaks)

Objectives
To investigate which factors collected in a specialized Cancer Fatigue Clinic (assessments, social circumstances, occupation and work, medical diagnoses) can predict a medium-term improvement in symptom burden, functional deficits and ability to work in the study population when a standardized intervention program is implemented?

Results 108 patients; 79% female, 54 years; 72 % Breast Cancer; 84% Chemotherapy

Number of patients: 209
Inclusion 143 (110 Female, 33 male; age 55 [median, mean], range 18-83
Exclusion 66 40 Psychiatric disease, 1 Fibromyalgia
5 Active Tumor, 6 no Tumor disease
14 missing dates of CFC
Cancer Fatigue Clinic First Consultation 1.5.2020 – 20.12.2024
Number of Consultations 3 (median, range 2-12 visits), 3.9 (mean)

Study population: 108 Patients with 2 or more Assessments
Time between First CFC and next CFC Visit (n=70) 70 days (median, range 14-533), 93 days (mean)
Time between First and last CFC 245 days (median, range 22-1112 days), 326 days (mean)

Age 54 [median, mean], range 21-79
Gender 85 female, 23 male
CFC first 1.5.2020 – 1.10.2024
Location 1000er 1, 2000er 1, 3000er 6, 4000er 18, 5000er 3, 6000er 13
7000er 3, 8000er 44, 9000er 16, D 3

Results All (n=88 with examination) CS had Neuropsychological impairments

Neuropsychological examination	88 (81%)	SIF cognitive	ESAS drowsiness
- 1=mild	15	6.6 (n=15)	4.7 (n=15)
- 2=mild-moderate	27	6.3 (n=26)	4.3 (n=26)
- 3=moderate	44	6.5 (n=43)	3.8 (n=43)
- 4=moderate-severe	2	8.5 (n =2)	3.5 (n=2)

Results 1/3 of CS: Insurance problems

. Prior Tumor before the latest tumor 15
. Tumor Type: 3 Lung incl. Adeno, SCC, SCLC, Mesohelioma (#1)
4 Upper GI incl. Pancreas & Gallbladder, (#2)
8 Lower (CRC, Anal) (#3)
5 Gyn (Uterus, Zervix, Ovar, et al.) (#4)
56 Breast (#5)
2 Urogenital (RCC, Urothel) (#6)
2 Prostate, Testic (#7)
15 Hematological (Lymphoma incl. Myeloma, Leukemia) (#8)
13 Other (Brain, HNO, Sarkoma, Skin, etc.) (#9; #0)

Anticancer treatment
. Chemo or Imm AND Radio AND Surgery 53 (no 55)
. Chemotherapy 84 (no 24)
- *Relationship with Fatigue* *84 (100%)*
. Immuntherapy 35 (no 73(
. Radiotherapy 68 (no 40)
- *Relationship with Fatigue* *57 (84%)*
. Surgery 95 (no 13), 1 Surgery 51, #2: 24, #3: 12
- *Relationship with Fatigue* *57 (60%) [26 possible, 31 clear)*
. Mistletoe 18 (no 77)
. Maintenance any 6 (no 102)

Cofactors

. Emotional burden	94 (87%)	no 14
- *Anxiety ESAS*	*4.2/10*	*1.9/10*
- *Depression ESAS*	*3.7/10*	*2.1 /10*
. Pain syndrome	62 (57%)	no 46
. CINP	32 (30%)	
. Sleep Disorder	72 (67%)	no 36
- *SIF Sleep Helpful*	*5.9/10*	*4.2/10*
. Malnutrition	35 (32%)	
. Thyroid	20 (19%)	
. Hypogonadism	4 (4%)	
. Covid	43 (40%)	
. Heart Disease	9 (8%)	
. Rheumatic disease	17 (16%)	
. Chronic inflammation	18 (17%	
. Other	84 (78%)	

Results All outcomes improved from 1st to last CFC (p<.001; SWE p=.043, DT p=.030), except ESAS wellb., fatigue, and anxiety, SkPTBS, Coherence, WHODAS.

	Baseline	next visit	last visit	T-Test BL vs Last visit
		(n=68)	*(n=107)*	*(2-sided, paired)*
ESAS fatigue number 0-10	6.63 *(n=108)*	6.65	6.30	ns (p=.127)
. Score 0-4	12 (11%			
. Score 5	21 (19%)			
. Score 6	13 (12%)			
. Score 7-10	62 (57%)			
ESAS drowsiness number 0-10	3.92 *(n=105)*	3.87	3.65	p<.001
. Score 0-4	58 (55%			
. Score 5	10 (10%)			
. Score 6	16 (15%)			
. Score 7-10	21 (20%)			
. Missing	3			
SIF overall 0-10	6.47 *(n=104)*		6.49	5.72 p=.001
. Score 0-4	14 (13%			
. Score 5	12 (12%)			
. Score 6	27 (26%)			
. Score 7-10	51 (49%)			
. Missing	4			
SIF cognitive 0-10	6.54 *(n=104)*		6.52	5.87 p<.001
. Score 0-4	18 (17%			
. Score 5	13 (13%)			
. Score 6	15 (14%)			
. Score 7-10	58 (56%)			
. Missing	4			
SIF emotional 0-10	3.64 *(n=104)*		3.55	2.55 p<.001
. Score 0-4	67 (64%)			
. Score 5	7(7%)			
. Score 6	7(7%)			
. Score 7-10	23 (22%)			
. Missing	4			
SIF physical 0-10	6.06 *(n=104)*		5.59	4.92 p<.001
. Score 0-4	28 (27%)			
. Score 5	13 (13%)			
. Score 6	11 (11%)			
. Score 7-10	52 (50%)			
. Missing	4			

	Baseline	last visit
		(n=107)
SkPTBS overall score 0-166	62.5 *(n=50)*	62.4
. Score 0-49 kein Verdacht	21 (42%)	
. Score 50-81 Verdacht	12 (24%)	
. Score 82-115 hoher Verdacht	12 (24%)	
. Score ≥ 116 dringender Verdacht	5 (10%)	
. Missing	58	
SWE overall score 10-40	26.1 *(n=86)*	27.3
. Score 10-19	12 (14%)	
. Score 20-29	49 (57%)	
. Score 30-40	25 (29%)	
. Missing	22	
Coherence Sum	35 *(n=92)*	3.5
. Score 0-29	19 (21%)	
. Score 30-39	48 (52%)	
. Score 40-52	25 (27%)	
. Missing	16	
Coherence manageability 0-20	10.9	7.9
Coherence reflection 0-16	10.1	7.3
Coherence balance 0-16	8.9	6.5
ESAS wellbeing 0-10	5.1 *(n=108)*	4.6
. Score 0-4	42 (39%)	
. Score 5	21 (20%)	
. Score 6	17 (16%)	
. Score 7-10	28 (26%)	
Distress Thermometer 0-10	5.8 *(n=96)*	4.5
. Score 0-3	9 (9%)	
. Score 4	6 (6%)	
. Score 5	12 (13%)	
. Score 6, 6.5	15 (16%)	
. Score 7, 8	39 (41%)	
. Score 9, 10	15 (16%)	
. Missing	12	
BFI overall score 9-90	47.6	39.2
DICRFS overall score 0-12	9.5 *(n= 99)*	7.8
. Score 0-5	4 (0.4%)	
. Score 6-9	19 (19%)	
. Score 10-11	40 (40%)	
. Score 12 /12	36 (36%)	
. Missing	9	
FTSTS seconds (number)	6.7	4.8
. SIF Physical Score 0-6	6.9* *(n=43; 9 missing I*	
Score 7-10	9.8* *(n=40, 12 missing*	

	Baseline	last visit
		(n=107)
ESAS anxiety 0-10	3.9 *(n=108)*	3.6
. Score 0-3.5	56 (52%)	
. Score 4	7 (0.6%)	
. Score 5	13 (12%)	
. Score 6	14 (13%)	
. Score 7-10	18 (17%)	
ESAS depression 0-10	3.5 *(n=108)*	2.7
. Score 0-3.5	62 (57%)	
. Score 4	12 (11%)	
. Score 5-6.5	12 (11%)	
. Score 7-10	22 (20%)	
HADS A 0-21	8.6 *(n=106)*	7.5
. Score 0-9	61 (58%)	
. Score 10-12	26 (25%)	
. Score 13-21	19 (18%)	
. Missing	2	
HADS-D 0-21	7.8 *(n=106)*	6.8
. Score 0-9	72 (68%)	
. Score 10-12	10 (0.9%)	
. Score 13-21	24 (23%)	
. Missing	2	
BAI overall score 0-63	11.4 *(n= 64)*	14.5
. Score 0-7	10 (16%)	
. Score 8-15	14 (22%)	
. Score 16-25	23 (36%)	
. Score 26-63	17 (27%)	
. Missing	44	
BDI II overall score 0-63	16.4 *(n=103)*	13.9
. Score 0-13	31 (30%)	
. Score 14-19	40 (39%)	
. Score 20-28	23 (22%)	
. Score >28	9 (9%)	
. Missing	5	

Results Multi-Modal Cancer Treatment correlated significantly with ESAS-Fatigue, SIF-cognitive, and BFI

Multimodal anticancer Tx (Chemo/Immune AND Radioth AND Surgery) **and Fatigue**

	Pearson-Corr	Sign (2-sd)
. ESAS Fatigue	.210	**.029**
. ESAS drowsiness	.135	.169
. SIF overall	.188	.056
. SIF cognitive	.318	**.001**
. SIF emotional	.135	.172
. SIF physical	.044	.657
. BFI overall score	.281	**.004**

Results Optimal MMFI (all MMFI elements done) was at first CFC in 2%, at last CFC in 62%; recommendation for ≥3 MMFI occurred in 43% and 9%, respectively.

	@ Baseline *(n=108)*	last CFC visit *(n=108)*
Multimodal Tx Discussion		
. 0= not mentioned	60 (58%)	15 (14%)
. 1 = some activities, but not all or not sufficient	42 (40%)	26 (24%)
. 2 = multimodal without over- or under-training)	2 (2%)	66 (62%)
. Missing	4	1
Multimodal Tx Discussion "perfect"		
. 0= perfect, no adaptations needed, all elements done	2 (2%)	66 (62%)
. 1= not yet optimal	102 (98%)	41 (38%)
Multimodal Tx next steps		
. 0 = not mentioned no single intervention recommended)	6 (6%)	49(46%)
. 1 = recommend to add/improve one element	15 (14%)	28 (26%)
. 2 = recommend to add/improve two elements	39 (37%)	20 (19%)
. 3 = recommend to add/improve ≥three elements)	46 (43%)	10 (9%)
. Missing	2	2
Multimodal Tx next steps "perfect"		
. 0= perfect no recommendation needed	6 (6%)	49 (46%)
. 1= recommended one, two , three or more	102 (92%)	58 (44%)
. Missing	2	2

Interventions	@ Baseline *(n=108)*	next CFC Visit *(n=69)*	last CFC visit *(n=108)*	
Physical Activity				
. 0 = none reported	6	0	3 (3%)	
. 1 = low intensity (walking only)	36 (35%)	11 (19%)	19 (18%)	
. 2 = moderate with some higher intensity activities	39 (38%)	21 (36%)	44 (43%)	
. 3 = formal training (2-3 x / week) self, MTT, other)	21 (21%)	26 (45%)	37 (36%)	
. Missing	6	11	5	
Mind/Body				
. 0 = none reported	39 (38%)	14 (24%)	21 (20%)	
. 1 = low intensity (breathing or meditation, etc. infrequently)	23 (23%)	11 (19%)	17 (17%)	
. 2 = moderate (several times per week)	24 (24%)	21 (36%)	41 (40%	
. 3 = formal activities (Yoga lectures, Qi-Gong, etc.))	16 (16%)		12 (21%)	24 (23%)
. Missing	6	11	5	
Energy Mgmt				
. 0 = none reported	64 (63%)	13 (22%)	18 (17%)	
. 1 = informal	35 (34%)	28 (48%)	57 (55%)	
. 2 = formal (including documentation)	3 (3%)	16 (28%)	24 (23%)	
. 3 = with ergotherapy (or other professional) support)	0		1 (2%)	4 (4%)
. Missing	6	11	5	
Psychological				
. 0 = non reported	47 (46%)	28 (48%)	46 (45%)	
. 1 = low intensity (as needed psychologist or other)	11 (11%)	3 (5%)	11 (11%)	
. 2 = moderate intensity (planned, monthly or more)	43 (42%)	23 (40%)	43 (42%)	
. 3 = formal structured weekly or biweekly)	1 (1%)	4 (7%)	3 (3%)	
. Missing	6	11	5	
Nutrition				
. 0 = not reported	34 (33%)	29 (50%)	24 (23%)	
. 1 = no adaption to disease	6 (6%)	1 (2%)	2 (2%)	
. 2 = some adaptations (legumes, healthy, etc.)	56 (55%)		24 (41%)	49 (48%)
. 3 = formal fatigue-focused (protein-rich, antiinflammatory, etc.)	6 (6%)	4 (7%)	27 (26%)	
. Missing	6	11	5	
Sleep				
. 0 = not reported	91 89%)	45 (78%)	75 (73%)	
. 1 = some sleephygiene	8 (8%)	7 (12%)	17 (17%)	
. 2 = formal activities (sleep restriction, sleep time, etc.)	3 (3%)	6 (10%)	11 (11%)	
. Missing	6	11	5	
Art Therapy				
. 0 = none reported	95 (93%)	51 (88%)	95 (92%)	
. 1 = Music- or Art therapy	7 (7%)	7 (12%)	8 (8%)	
. Missing	6	11	5	
Body Treatment				
. 0 = none reported	88 (86%)	46 (79%)	84 (82%)	
. 1 = massage, craniosacral, Shiatsu, etc.	14 (14%)	12 (21%)	19 (18%)	
. Missing	6	11	5	
Physiotherapy				
. 0=none	85 (83%)	41 (71%)	79 (77%)	
. 1=mentioned	17 (17%)	17 (29%)	24 (23%)	
. Missing	6	11	5	

Conclusion

CS with Fatigue experience high **multidimensional symptom burden** and **neuropsychologi**al impairments, especially with more **intense anticancer treatment**

A **C**ancer **F**atigue **C**linic can achieve implementation of **MMFI daily habits** by visit recommendations;
CS with higher depressive symptoms, Distress, impairment by fatigue and physical fatigue achieve

A **M**ulti-**M**odal **F**atigue **I**ntervention **improves** many **symptom** and **function outcomes**, but ***not*** (subjective) ***disability*** and ***visual-analogue scale fatigue***.

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