

# First Patient Survey about Tumor-associated Fatigue in NEN

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## Background:

Tumor-related fatigue (TrF) is a debilitating condition occurring during the course of the tumor disease, and can persist despite tumor remission and completion of therapies. The syndrome consists of chronic fatigue, sleep disturbances, severe pain, brain-fog and is often underestimated by physicians. Potential pathomechanisms are an ongoing inflammation and other risk factors<sup>2</sup>. Diagnosis is made according to the criteria by D. Cella<sup>1</sup> (Figure 2).

## Aim:

The purpose of the survey was to figure out how many NEN patients suffer from TrF, if there are factors associated with fatigue, and how this impairs the patient's quality of life and working ability.

## Material and Methods:

The national German support group "Netzwerk Neuroendokrine Tumoren (NeT) e.V." conducted together with the scientific support of the Charité this first survey concerning fatigue among NEN patients. The survey was conducted completely anonymous via Link ("Survey Monkey") and email to all patients of the support group; in part, for patients without email account, the questionnaires were sent by post. Furthermore the survey was published on the Netzwerk NeT e.V. – homepage and distributed by physicians.

The questionnaires consist of several instruments to characterise the symptoms. We used the ICD-10 criteria by D. Cella<sup>1</sup> (Figure 2) and the LASA-Score, a single-item linear analog scale from 0 (no fatigue) to 10 (severe fatigue) to measure fatigue. For Quality of Life we used the EORTC QLQ-C30, a common instrument in the evaluation of cancer patients. Further the diagnostic criteria for Chronic Fatigue syndrome, the Canadian Criteria<sup>3</sup> were evaluated. The study was approved by the Ethics Commission of Charité-Berlin.

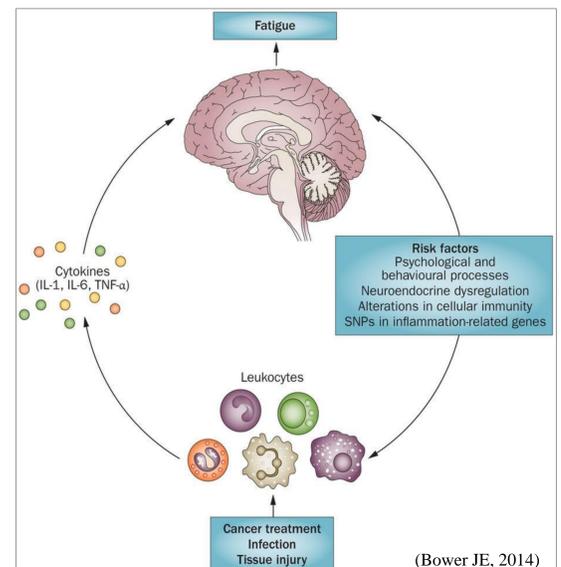
## Results:

Between 06/2017 and 09/2017 686 patients started the online survey, but only 69 % (470) finished the survey. 51 questionnaires returned by post. Overall 501 (73 %) replies could be evaluated.

Female (54 %) and male (44 %) patients were distributed even. The median age is 62. The most common entities were intestinal (42 %) and pancreatic (20 %) NEN (Figure 3). The most common therapeutics patients received at the time were biotherapeutics (Figure 4), mostly somatostatin analogues (42 %).

58% of the participants stated that they suffered from severe fatigue in the past or ongoing. The proposed diagnostic criteria by Cella were fulfilled in 41 %, most of them were currently under no cancer therapy. Nearly half of the patients with NEC G3 and 41 % with NET G1/G2 tumors meet the Cella criteria. In the EORTC-subscore "quality of life" patients with self reported fatigue scored significantly (p-value < 0.05) worse than patients without fatigue. This is also represented in the negative correlation between quality of life and the LASA-Score (r = -0.64) (Fig. 5). Also in the subscore "social function" patients with fatigue score significantly lower (p-value < 0.05). Patients are impaired in the ability to work. 6 % had to reduce worktime because of their disease and 21 % had to retire.

8 % patients also match the criteria for "Chronic Fatigue Syndrome". 23% of the patients suffer from post exertional malaise (PEM), in which symptoms of fatigue, pain and dizziness can worsen dramatically even after a small mental or physical exertion.



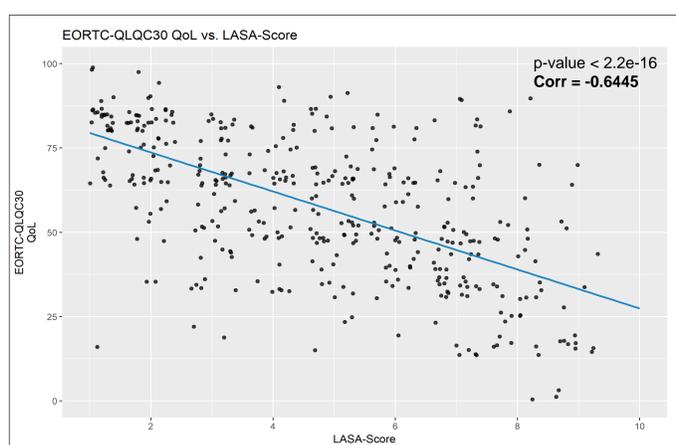
**Figure 1:** Elevated levels of proinflammatory cytokines like IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 are found in patients with TrF. These cytokines can lead to a wide variety of symptoms, like fatigue and other behavioural changes caused by their effect on the central nervous system<sup>2</sup>.

- A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level  
A2. Complaints of generalized weakness or limb heaviness  
A3. Diminished concentration or attention  
A4. Decreased motivation or interest to engage in usual activities  
A5. Insomnia or hypersomnia  
A6. Experience of sleep as unrefreshing or nonrestorative  
A7. Perceived need to struggle to overcome inactivity  
A8. Marked emotional reactivity (eg, sadness, frustration, or irritability) to feeling fatigued  
A9. Difficulty completing daily tasks attributed to feeling fatigued  
A10. Perceived problems with short-term memory  
A11. Postexertional malaise lasting several hours  
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning  
C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.  
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

**Figure 2:** Proposed ICD-10 criteria for cancer related fatigue by Cella<sup>1</sup>. At least six of the symptoms (A1 – A11) have to be present nearly every day during the same two-week period in the past month. A1 needs to be present.

	n = 501		
	f	m	NA
<b>Gender (%)</b>	272 (54 %)	221 (44 %)	8 (1%)
<b>Age (median + STD Min - Max)</b>	59 $\pm$ 11 26 - 84	63 $\pm$ 10 22 - 82	3
<b>Metastasis at Diagnosis (%)</b>	yes	no	NA
	289 ( 57 %)	161 (32 %)	51 (10%)
<b>Grading at Diagnosis (%)</b>	G1 or G2	G3	NA
	430 (85 %)	60 (11 %)	11 (2%)
<b>currently under Therapeutics (%)</b>	yes	no	NA
	278 (55 %)	193 (38 %)	30 (5%)
<b>EORTC-Quality of Life (median + STD)</b>	<b>Fatigue</b>		NA
	yes	no	NA
<b>EORTC-cognitive Function (median + STD)</b>	50 $\pm$ 21.96	75 $\pm$ 18.3	24 (4%)
<b>EORTC-social Function (median + STD)</b>	66.67 $\pm$ 26.22	100 $\pm$ 15.89	116 (23%)
<b>EORTC-social Function (median + STD)</b>	66.67 $\pm$ 35.05	83.33 $\pm$ 21.46	160 (31%)

**Figure 5:** Characteristics of the study cohort. EORTC-function-scores range from 100 (best) to 0 (worst).



**Figure 6:** EORTC-QLQC30-QoL vs LASA-Score with linear regression. Pearson's product-moment: correlation corr = - 0.6445, p-value < 2.2e-16.

## Conclusion:

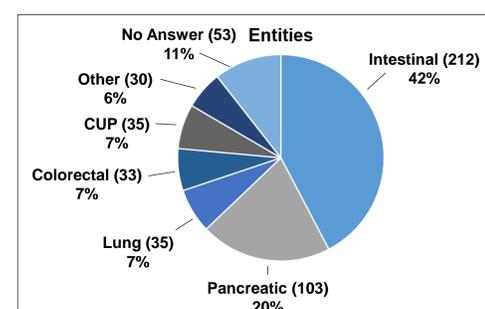
Fatigue is a major and very common symptom during and after therapy in NEN.

It's a major cause for low quality of life.

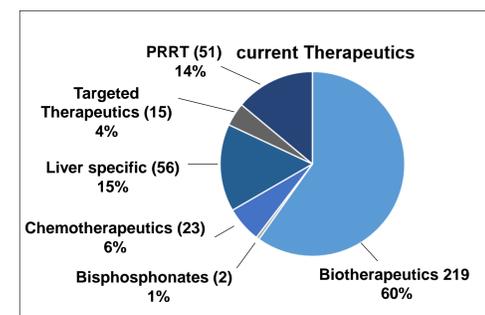
Since 1/5 of all participants reported a severe systemic exertion intolerance it seems that TrF is not a homogeneous disease. Patients may need individualized therapy to get better (probably adapted sport recommendation).

## Summary:

- 58 % of questioned NEN-patients suffered at some point of their disease from significant fatigue.
- All subtypes of NEN are affected.
- Multimodal integrative approaches are necessary to achieve improvement of quality of life.



**Figure 3:** Entities of the first tumor localization.



**Figure 4:** Current treatment (biotherapeutics include interferon and somatostatin analogues; chemotherapeutics include Temozolomid, Etoposid, 5-Fluorouracil; Liver specific include TACE, SIRT and RFA; targeted therapeutics include Everolimus, Sunitinib, Avastin).

## References:

1. Cella, D. et al. (2001) J Clin Oncol. 19(14):3385-91.
2. Bower, JE (2014) Nat Rev Clin Oncol;11(10):597-609.
3. Carruthers, BM et al. (2011) J Intern Med; 70(4):327-38.

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