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ORIGINAL ARTICLE

Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case–control study

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Abstract
Background Involuntary weight loss (IWL) is frequent in advanced cancer patients causing compromised anticancer treatment outcomes and function. Cancer cachexia is influenced by nutrition impact symptoms (NIS). The aim of this study was to explore the frequency of NIS in advanced patients and to assess specific interventions guided by a 12-item NIS checklist.
Methods Consecutive patients from an outpatient nutrition-fatigue clinic completed the NIS checklist. The NIS checklist was developed based on literature review and multiprofessional clinical expert consensus. Chart review was performed to detect defined NIS typical interventions. Oncology outpatients not seen in the nutrition-fatigue clinic were matched for age, sex, and tumor to serve as controls.
Results In 52 nutrition-fatigue clinic patients, a mixed cancer population [IWL in 2 months 5.96 % (mean)], the five most frequent NIS were taste and smell alterations 27 %, constipation 19 %, abdominal pain 14 %, dysphagia 12 %, and epigastric pain 10 %. A statistically significant difference for NIS typical interventions in patients with taste and smell alterations ($p = 0.04$), constipation ($p = 0.01$), pain ($p = 0.0001$), and fatigue ($p = 0.0004$) were found compared to the control population [mixed cancer, 3.53 % IWL in 2 months (mean)].
Conclusion NIS are common in advanced cancer patients. The NIS checklist can guide therapeutic nutrition-targeted interventions. The awareness for NIS will likely evoke more research in assessment, impact, and treatment.

Keywords Cachexia · Anorexia · Nutrition · Cancer · Nutrition impact symptoms · PG-SGA

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1 Introduction

Cancer cachexia affects a majority of cancer patients and has a considerable negative impact on quality of life, physical function, anticancer treatment response, and survival [1]. The lack of a common definition hindered the understanding of the cachexia pathophysiology and the development of treatment strategies [2]. An international consensus recently defined cancer cachexia as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology of cancer cachexia is characterized by a negative protein and energy balance due to a variable degree of reduced food intake and deranged metabolism [3]. Currently, there is no standard treatment for cachexia available [4].

A number of symptoms and complications of advanced cancer, anticancer treatment, or medical co-morbidities [5] can interfere with patients' appetite and ability to eat or digest food [6]. The broad spectrum of impediments to oral nutritional intake can be conceptualized as nutrition impact symptoms (NIS) [7].

NIS seem to occur frequently in clinical care [8], such as taste and smell alterations [9], mucositis [10], nausea [11], constipation [12], pain and its treatment [13], or shortness of breath [14]. Despite the impact of these causes on oral nutritional intake, they have rarely been systematically assessed and original research has so far focused either on brief nutritional screening instruments or on comprehensive assessments of nutritional problems [15]. The systematic assessment and treatment of NIS merits further evaluation since the majority of these symptoms can be treated by supportive care measures and their negative impact on oral nutritional intake may be potentially halted [16]. Widely used nutrition assessment instruments such as the PG-SGA (Patient-Generated Subjective Global Assessment) cover NIS to some extent [17]. The PG-SGA assesses 14 symptoms that keep the patient from eating (anorexia, nausea, vomiting, constipation, diarrhea, mouth sores, dry mouth, problems with taste, smell, or swallowing, early satiety, pain, fatigue, and other reasons) [18]. An evaluation of the PG-SGA NIS assessment showed high numbers of patient-reported symptoms that keep them from eating, e.g., anorexia 47 %, early satiety 43 %, nausea 20 %, and abnormal taste 20 % [19]. A correlation between number of NIS and low nutritional status has been reported [20], and the PG-SGA does predict nutritional risk in patients receiving chemotherapy [21], hospital stay [22], and patient prognosis [23]. The score also leads to (overall) nutritional triage recommendations in patients having various tumor types [18], an important help considering that a recent survey of oncologists suggested that awareness of nutritional issues in oncology may merit improvement [24].

In a recent publication, the prevalence and relationship of NIS were evaluated in head and neck cancer patients by means of the PG-SGA. NIS such as anorexia, mouth sores, or dysphagia were found to be significant predictors of reduced oral dietary intake [7]. Although the PG-SGA covers these NIS, the assessment done by a healthcare professional generates a score based on four domains: history of weight loss, estimation of functional status, physical examination, and the list of 14 symptoms. Each of the 14 symptoms assessed in the PG-SGA is graded and adds between one and three points per symptoms (total of 24 points for the entire NIS checklist) to the global PG-SGA score. Whether NIS in the PG-SGA score will trigger specific interventions has not been tested and the relationship for the individual NIS and impaired oral nutritional intake is not fully understood [25].

This study aims to explore the patient-reported frequency of NIS in a mixed advanced cancer patient population by means of a subjective quantitative NIS checklist.

As an exploratory objective, we aim to generate evidence for the practice-guiding potential of the checklist.

2 Methods

The frequency of NIS was evaluated in a cross-sectional study of outpatients. To appraise the practice-guiding potential, a case–control study in the outpatient clinic was performed. The study was approved by the local ethics review board.

2.1 NIS checklist

This first version of the NIS checklist was developed based on a literature review, multiprofessional clinical expert opinions, and clinical experience. The checklist was piloted and continuously improved. A number of clinical symptoms and syndromes having a potential negative impact on oral nutritional intake were included.

Anorexia and early satiety were considered to be directly cachexia associated and therefore not included in the checklist (Table 1). Eight symptoms potentially affect the function or integrity of the gastrointestinal tract from mouth to anus: stomatitis, taste and smell alterations dysphagia, epigastric pain, abdominal pain, constipation, diarrhea, and defecation after meal. Four other complex syndromes can be associated with decreased nutritional intake: pain, dyspnea, fatigue, and depression/anxiety. In order to keep the checklist short, an open question was added in order to allow patients to report individual-specific NIS.

Table 1 Translation of version 1 of the NIS checklist as used in this study

I have reduced appetite and/or reduced oral intake because of	None (1)	Little (2)	Moderate (3)	A lot (4)
Stomatitis				
Taste and smell alterations				
Dysphagia				
Pain in the stomach				
Abdominal pain				
Constipation (better appetite after bowel movements)				
Diarrhea				
Defecation after meals				
Pain				
Dyspnea				
Fatigue				
Other reasons				

The final checklist consists of one page and the items are filled in by the patients. A four categorical scale was chosen. Patients answered 12 questions "I have reduced appetite and/or reduced oral intake because of each of the symptoms", e.g., taste and smell alterations by checking one of the four choices: 1 = none, 2 = little, 3 = moderate, 4 = a lot. A threshold of three or more was chosen and considered significant for this study based on clinical experience and patients' interviews in the development phase.

2.2 Patient populations

Case patients The first group included subjects from the nutrition-fatigue clinic, which is a specialized interdisciplinary outpatient clinic for advanced cancer patients, having as predominant problems one or more of the following: involuntary loss of weight, appetite, or fatigue. Family members are an important component of the nutrition-fatigue clinic evaluation. The aim of this clinic is to perform multidimensional in-depth assessments by specialized nurses, nutritionists, psycho-oncologists, and palliative oncology specialists, tapping the potential of interdisciplinary team interactions, as well as offering tailored symptom control. Predefined assessment instruments include the Edmonton Symptom Assessment Scale [11 categorical scale (0 = none, 10 = worst)] [26], NIS checklist, screening questions for eating-related distress [27], Hamilton Anxiety/Depression Scale [28], three single-item fatigue-domain questions [29], 2-day food protocols, and a structured interview for the social support situation [30].

Control patients We matched patients from the routine medical oncology outpatient clinic, retrieved from the alphabetical electronic database by hand-search starting at "A". Patients were matched for tumor type (using the etiological groups—gastrointestinal, urogenital, lung, breast, prostate, mesothelioma, lymphoma, and ear–nose–throat), age (decade), tumor stage (I–IV), and gender. Symptom severity was assessed by the treating oncologists by means of a five categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = strong, 4 = very strong) as routinely used since many years. To retrieve patients comparable to the patients from the nutrition-fatigue clinic, the inclusion criteria for the control patients were either fatigue or anorexia [rated as mild (1) to very strong (4)] or documented IWL (>2 % in 2 months or >5 % in 6 months). In none of the control patients the NIS checklist was used.

2.3 Frequency of NIS

The number of patients from the nutrition-fatigue clinic having scores of the NIS checklist above the threshold of 3 or more was assessed.

2.4 Case–control comparison of a practice-guiding potential of the NIS checklist

The charts of the matched patients from the nutrition-fatigue clinic and the routine oncology outpatient clinics were reviewed for the period of 2 weeks before and 2 weeks after the inclusion time point by two researchers applying a structured assessment template. Therapeutic interventions for NIS were defined as either:

1. Intention to ameliorate anorexia or cachexia specifically mentioned by the physician, or
2. Change or new onset of medication (e.g., laxatives, mouth care) or therapeutic counseling (e.g., nutritional, physiotherapy) for stomatitis, taste and smell alterations, dysphagia, epigastric or abdominal pain, constipation or diarrhea, or symptom control of pain, dyspnea, or fatigue.

Inconsistent chart review findings were discussed until consensus was reached (AO, FS, JW).

3 Statistical analysis

The distribution of age as well as weight loss, body mass index (BMI), and C-reactive protein by patient cohort were analyzed using a Mann–Whitney *U* test, while the distributions of gender by cohort was compared using a chi-square test.

To compare system load score among the two cohorts, all scores were standardized to a scale from 0 to 100. A Mann–Whitney *U* test was then performed on each of the symptom scores separately to assess if there were significant differences among the cohorts.

Comparison of frequency of intervention for each symptom was also performed using Fisher's exact test on a per symptom basis, and p values were adjusted using the Bonferroni correction.

The number of identified therapeutic interventions for NIS was compared between the patients treated in the nutrition-fatigue clinic and the case-matched controls. All analysis was performed in the R programming language.

4 Results

Patients from the nutrition-fatigue clinic and the control patients were all outpatients. As the control patients were matched (age, sex, and tumor type), no differences are reported regarding these parameters. CRP did not differ significantly in the two groups ($p = 0.68$); however, patients from the nutrition-fatigue clinic had a significantly lower body mass index (BMI, $p<0.0001$) and a trend towards

weight loss was seen (p=0.056) (Table 2). All patients had advanced tumor stage III or IV. No data on survival of these patients are available.

Standardized symptom load scores were compared. For anorexia and dyspnea, the two groups were comparable (p = 0.44 and 0.63, respectively). For pain (p<0.0001), nausea (p = 0.003), and fatigue (p = 0.002), a statistically significant higher symptom load was seen in the nutrition-fatigue clinic patient population compared to the control patients (Table 3).

4.1 Frequency of NIS

The most frequent patient-reported NIS in the nutrition-fatigue clinic patients were taste and smell alterations (27 %), constipation (19 %), abdominal pain (13.5 %), and dysphagia (11.5 %) (Table 4). Very few NIS were reported to the open question, among which nausea, emesis, general anxiety, and uncertainty were mentioned in single cases.

Of the nutrition-fatigue clinic patients, 19 (37 %) reported no relevant NIS (score 1 or 2 on checklist), 15 patients (29 %) one, 11 patients (21 %) two, and seven patients (13 %) three or more NIS.

4.2 Case–control comparison of the NIS-specific interventions

Patients in the nutrition-fatigue clinic received therapeutic interventions for the same symptom statistically significant more often than matched control patients (Table 5), e.g., taste and smell alterations (p = 0.04), constipation (p = 0.01), pain (p = 0.0001), and fatigue (p = 0.0004). For NIS such as stomatitis, dysphagia, or diarrhea, the number of patients and interventions were too small to detect differences in specific actions taken.

5 Discussion

This study reports patient's subjective rating of the impact of NIS on their appetite or oral nutritional intake. Moderate to high impact of NIS on oral intake was reported frequently in this population of patients with mixed advanced cancer. Assessment of NIS seems feasible and has the potential to trigger symptom-specific interventions or examinations.

Table 2 Patient characteristics for patients from the nutrition-fatigue clinic and the matched control patients

	Nutrition-fatigue clinic (n=52)		Control patients (n=52)		p value
Age, years					
Median	63		64		
Range	25–86		26–81		0.35
Sex					
Male	31		31		
Female	21		21		0.99
Primary tumor site	*N*	%	*N*	%	
Gastrointestinal *n* (%)	16	31	16	31	
Urogenital *n* (%)	2	4	2	4	
Lymphoma *n* (%)	6	12	6	12	
Breast *n* (%)	4	8	4	8	
Lung *n* (%)	11	21	11	21	
ENT *n* (%)	3	4	3	4	
Prostate *n* (%)	9	17	9	17	
Mesothelioma *n* (%)	1	2	1	2	
C-reactive protein (CRP, mg/l)					
Median	13		11		0.68
Range	1–115		1–132		
Mean body mass index (kg/m^2)	22.4±3.7		24.9±3.7		0.0001
Range	14.5–31.3		17.3–34.3		
Patients with weight loss ≥2% in prior 2 months (*N*/%)	28/70 %		28/70 %		
Mean value of weight loss in prior 2 months (%)	4.7		2.8		0.056
Range	−8.9–32.9		−3.8–14.8		

Table 3 Symptom load in the nutrition-fatigue clinic patients compared to the matched patient population

Symptom load (mean ± SD):	Nutrition-fatigue clinic (n=52)	Control patients (n=52)	p value
Anorexia	32.7±23.4	30.4±18.9	0.44
Pain	53.8±29.3	17.9±18.5	<0.0001
Fatigue	52.5±28.4	26.0±29.3	0.002
Nausea	17.9±23.3	5.9±13.8	0.003
Dyspnea	11.7±19.2	11.7±19.2	0.63

In advanced cancer patients, NIS are very common reaching up to 50 %, taste and smell alterations being the most common reaching almost 30 %. Not astonishingly, patients admitted to a specialized nutrition-fatigue clinic presented with higher NIS load (taste and smell alterations, dysphagia, and constipation) than the controls in the oncology outpatient clinic. A recent study in a cancer cachexia center confirmed the frequent occurrence of two to three NIS per patient and its association with poor appetite and weight loss [31].

Most of the reported symptoms were of gastrointestinal origin such as constipation or taste and smell alterations. Patients in our study mentioned constipation as related to impaired nutritional intake in 20 %. In a previous head and neck cancer study population, 10 % of patients related constipation to reduced oral nutritional intake [7]. It can be hypothesized that in selected tumor types, specific NIS might be more common such as dysphagia and mouth sores in head and neck cancer patients for instance. In our mixed cancer population, head and neck cancer though accounted for 8 % of the total of patients only.

The reason for differences in the documented frequency in the nutrition-fatigue clinic patients compared to the control patients might be that most of these symptoms are not routinely assessed in the local oncological outpatient clinic and/or are not documented in the charts. In case of NIS routinely assessed in a specialty oncological outpatient clinic, the frequency of interventions in patients is comparable (e.g., dysphagia, diarrhea). In contrast, silent symptoms such as taste and smell alterations or even fatigue seem to be frequent but are not always brought forward by the patient or assessed by the oncologist. For symptoms with few therapeutic options, the oncologists might not ask the patient about it unless it is reported spontaneously. The early recognition and treatment of silent symptoms may limit their contribution to the cachexia syndrome.

The use of the NIS checklist in the nutrition-fatigue clinic triggered more therapeutic interventions compared with the control population (Table 5). The highest incidence of reported interventions with a significant difference compared to the control patients was seen in taste and smells alterations (85 % vs. 14 %), constipation (100 % vs. 45 %), pain (100 % vs. 57 %), and fatigue (80 % vs. 42 %).

This is, to our knowledge, the first study to systematically assess and report NIS-specific interventions. This approach was chosen in order to evaluate the triggered NIS-specific interventions leading ideally to better symptom control. While the effectiveness of NIS-specific interventions was not assessed in our study, it can be hypothesized that interventions may positively impact nutritional intake.

A major limitation is the development of the checklist. It has to be noted that anorexia and early satiety and a number of symptoms potentially affecting appetite such as nausea, vomiting, or depression were not included. Most causes assessed with the NIS checklist could also be evaluated using the PG-SGA [15]. It can be argued that the use of the widely used PG-SGA would have generated more comparable results. Our checklist was based on literature review and expert opinion and continuously tested in our clinic. Similar other tools are being used in other clinics (e.g., MD Anderson Cancer Center) and a common standard is not yet established.

The rating of the specific impact on nutritional intake of different symptoms at the same time may be too complex for

Table 4 Frequency of nutrition impact symptoms (NIS) rated as 3 (moderate) and 4 (a lot) by the NIS checklist in patients assessed in the nutrition-fatigue clinic

	Nutrition-fatigue clinic (n=52; percentage)	
	N	%
Stomatitis	4	7.7
Taste and smell alterations	14	26.9
Dysphagia	6	11.5
Epigastric pain	5	9.6
Abdominal pain	7	13.5
Constipation	10	19.2
Diarrhea	4	7.7
Defecation after meal	3	5.8
Pain	3	5.8
Dyspnea	0	0
Fatigue	5	9.6

Table 5 Comparison of the frequency of NIS in the nutrition-fatigue patient population and in the control population

Nutrition impact symptoms Frequency and interventions	Nutrition-fatigue clinic $n=52$	Control patients $n=52$	p value
Patients with stomatitis (n)	4	3	
Patients with interventions (n)	3	1	0.49
Patients with taste and smell alterations (n)	14	7	
Patients with interventions (n)	12	1	0.04
Patients with dysphagia (n)	6	3	
Patients with interventions (n)	6	2	0.99
Patients with epigastric pain (n)	5	3	
Patients with interventions (n)	3	2	0.99
Patients with abdominal pain (n)	7	6	
Patients with interventions (n)	6	2	0.10
Patients with constipation (n)	10	11	
Patients with interventions (n)	10	5	0.01
Patients with diarrhea (n)	4	6	
Patient with interventions (n)	3	4	0.56
Patients with defecation after meal (n)	3	0	
Patients with interventions (n)	3	0	0.99
Patients with pain (n)	3	28	
Patients with interventions (n)	3	16	0.0001
Patients with fatigue (n)	5	19	
Patients with interventions (n)	4	8	0.0004
Patients with dyspnea (n)	0	15	
Patients with interventions (n)	0	5	n.a.

an advanced cancer population. To encounter this, the actual version of checklist in use in our clinics is asking in a two-step procedure whether a symptom was present in the past 7 days and in a second step whether it had an impact on oral nutritional intake. However, symptoms should be treated regardless of their impact on oral intake.

Other limitations are the mixed cancer patient population in which the NIS assessment was performed resulting in different numbers of NIS and the use of chart review, which was carried out retrospectively and bears therefore the risk of selection bias. Furthermore, it must be taken into account that patients referred to a specialized dedicated nutrition-fatigue clinic are likely to have a higher symptom load. Also, the awareness of healthcare professionals in a specialized clinic may result in higher frequency of symptom assessment and treatment. Therefore, the relative impact of the checklist cannot be conclusively derived from our data.

The results of our study show that the awareness for NIS rise with the use of the NIS checklist, and it seems to trigger more therapeutic interventions compared to the matched control patients who are treated with standard care in the oncological outpatient clinic. In view of the long list of potential NIS, further research is needed on the relative importance of the single symptoms. Intervention studies are also needed to evaluate the impact of interventional management of NIS on improving nutritional intake. Standardization of NIS assessment is warranted to raise awareness of these possible correctable causes.

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