

Components of the anorexia–cachexia syndrome: gastrointestinal symptom correlates of cancer anorexia

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Abstract

Introduction Cancer-related anorexia is traditionally considered part of a complex but ill-defined anorexia–cachexia syndrome in which anorexia is intimately associated with other gastrointestinal (GI) symptoms and weight loss. We surveyed cancer patients with anorexia to learn more about the relationship between anorexia and these symptoms.

Materials and methods A 22-item GI questionnaire assessed the severity of anorexia and the prevalence of concurrent GI symptoms, including taste changes, food aversions, altered sense of smell, and diurnal food intake changes. The relationship between anorexia severity and anticancer therapy and prior menstrual or pregnancy-related appetite changes was also assessed.

Results Ninety-five of 101 patients with anorexia surveyed had complete data. Seventy-eight percent of them had

moderate or severe anorexia. Abnormal diurnal appetite variation, taste changes, and food aversions were present in over 50% of all those with anorexia. Judged by the numerical rating scale, the worse the anorexia, the more prevalent were early satiety, constipation, vomiting, and food aversions. Those with more severe anorexia had greater weight loss, and worse performance status. Anorexia severity did not correlate with that during prior menses/pregnancy or antitumor therapy.

Conclusions Evaluation of multiple other GI symptoms is important in understanding the total experience of cancer anorexia. Early satiety, taste changes, food aversions, and altered sense of smell are important accompanying GI symptoms. Most validated anorexia tools do not assess these commonly associated GI symptoms. Future research should develop a comprehensive anorexia symptom questionnaire.

Keywords Anorexia · Cancer · Gastrointestinal · Symptoms · Palliation · Cachexia

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Introduction

Anorexia and weight loss are a common cause of cancer morbidity and mortality. Up to 40% have anorexia at diagnosis and 80% in advanced disease [8, 9, 12, 36, 44]. In 1,000 consecutive patients referred to our palliative medicine program, over 60% had anorexia [44]. Normal appetite requires coordination of gustatory, neural, and humoral signals that regulate gastrointestinal (GI) hormones and motility. Both central and peripheral appetite signals are disordered in animal cancer models [13]. The pathogenesis of human cancer anorexia, however, is poorly understood but appears multifactorial [13]. Cancer anorexia likely results from altered peripheral hypothalamic signals

and neurohormonal mediators due to upregulated cytokines and eicosanoids and dysregulated monoamines [13]. Cancer treatment, co-medications, and psychologic stress contribute to its prevalence and probably to severity [26, 29, 30].

The presence of anorexia and involuntary weight loss has been termed the anorexia/cachexia syndrome (ACS) [25]. Clinically, this appears to vary from predominant anorexia to predominant weight loss. Significant involuntary weight loss may occur with little anorexia or severe anorexia with minimal weight loss. The ACS differs from starvation; appetite is absent or impaired in ACS, but present or enhanced in starvation. There is little information and no consensus on what exactly constitutes the anorexia–cachexia syndrome. Anorexia does not appear to be an isolated symptom but perhaps part of a symptom complex that include other GI symptoms, including taste and smell changes and altered circadian (diurnal) eating patterns and food aversions [3, 4, 16, 22, 23, 28, 37, 42]. We hoped that by collecting a more detailed symptom profile of those with cancer and anorexia, this might suggest clues to the pathophysiology of the syndrome and provide avenues for future research. We conducted a prospective observational survey to clarify the total GI symptom profile of cancer anorexia.

Methodology

Patient characteristics

Eligible patients with cancer and anorexia were invited to participate. After completing a numerical rating scale (NRS) for anorexia (0—no appetite and 10—normal appetite), an empirical questionnaire developed by the Palliative Medicine Research and Clinical Team was then completed by eligible patients. Patients had to be 18 or older and cognitively intact. This observational study was approved by the Cleveland Clinic Institutional Review Board.

Data collection

The anorexia questionnaire (Fig. 1) was empirically designed based upon prior studies by our group [20, 21]. The survey assessed anorexia severity based upon a numerical scale (0 = no appetite, 10 = normal appetite) and a categorical scale (mild, moderate, severe). Patient-estimated weight loss, diurnal appetite pattern, food aversion, other GI symptoms including taste and smell changes, prior anticancer therapy, patient concerns (and in women, a history of anorexia during pregnancy or menses) were also assessed. Smell and taste were not objectively tested. Symptoms are reported in the text in their order of overall prevalence. Interviews were by specialist attending

physicians or palliative medicine fellows. The presence of cachexia was evaluated by a global assessment by conventional clinical examination of general physical appearance. Muscle strength was not addressed. All data were entered on an Excel (Microsoft, Redmond, Washington) spreadsheet. Data were encoded in a Microsoft Access® database and analyzed using SAS® software (SAS Institute, Cary, NC, USA).

Statistical methods

Primary analysis was based on the NRS. Descriptive statistics were summarized as frequency and percentages for categorical variables and mean, standard deviation, median, and range for continuous variables. Logistic regression analysis was performed to determine the association between appetite loss (in numerical or categorical scale) and other symptoms. Two-sample *t* test or one-way analysis of variance (ANOVA) was used to compare NRS score to categorical covariates. Pearson correlation coefficients were estimated and tested for significance between NRS scores and continuous covariates. A Jonckheere–Terpstra trend test compared appetite NRS to the category appetite rating. The chi-square test compared symptom prevalence and primary site between men and women. All variables were included in a multiple regression model to see if any affected NRS scores. Numbers and percentages were rounded to the nearest whole number.

Results

Patient characteristics are in Table 1. One hundred and one non-consecutive eligible new patients with anorexia were surveyed over 5 months. All completed the survey. Six were excluded due to repeated assessments or incorrectly completed scales, as there was either a potential training effect or missing data. Ninety-five were evaluable. The median age was 63 years (range, 18–85) and 50 of 95 (52%) were female. Seventy-two percent (65/95) were Caucasian. Seventy-four percent (70/95) had documented metastatic disease. Twenty-three percent (22/95) had received chemotherapy and 11% (10/95) radiation therapy during the month before the survey. The mean Eastern Cooperative Oncology Group (ECOG) performance score (0–4) was 1.9 (SD=1.1). Eighteen percent (17/95) were taking corticosteroids and 4% (4/95) megestrol acetate at the time of the survey.

Gastrointestinal symptoms

Multiple GI symptoms were present simultaneously (in addition to anorexia) in 97% (Fig. 2); the most prevalent

Fig. 1 Anorexia questionnaire**ANOREXIA QUESTIONNAIRE**

Study # _____

Patient N# _____

CCF# _____

Date: _____

Patient Name: _____

Gender M F Age

Race: W AA H Other

Primary Diagnosis: _____

EOD BO BR LI LU LN

Other: _____

Current Medications:

1. Corticosteroids Yes No
2. Megestrol Acetate Yes No
3. Anabolic Steroid Yes No
4. Immunotherapy Yes No
5. In the last month:
 - Chemotherapy? Yes No
 - Radiotherapy? Yes No

ECOG

- 0 Normal activity, no limitation
- 1 Some limitation, in active work
- 2 Requires considerable assistance
- 3 Spend most of the day in bed
- 4 Very sick, rarely out of bed

1. How long has your appetite been reduced?
Days Months Years Don't know

were early satiety (82%), weight loss (79%), and taste changes (69%; Fig. 3). Most believed that their anorexia was caused by these GI symptoms (except hiccups).

Anorexia

Seventy-seven percent (64/95) still had hunger periodically despite the presence of anorexia. Forty-nine percent (47/95) had severe and 31% (29/95) moderate anorexia. Mean anorexia severity by NRS (0–10) was 3.6 (SD=2.3). There was more constipation ($p=0.04$), early satiety ($p=0.02$), food aversions ($p=0.003$), and vomiting ($p=0.01$) with lower

NRS scores, i.e., with more severe anorexia. Anorexia was present for >1 month in 77% (74/95). There was no relationship between cancer primary site and severity of anorexia. Those with severe anorexia by NRS were more likely ($p=0.004$) to be concerned about the symptom. This was also true for the categorical scale. Twenty-five percent were not personally bothered by their anorexia. Anorexia measured by the NRS was more severe in those with greater ($\geq 10\%$ versus $\geq 5\%$) weight loss even after adjustment for age, gender, and performance status ($p=0.06$).

Univariate analysis showed no statistically significant relationship between severity of anorexia and age,

Fig. 1 (continued)

2. **How would you rate the severity of your appetite loss?**
MI MO S Don't know
3. **On a scale (0=no appetite, 10 = normal appetite) choose the number that best describes your appetite today?**
 0 1 2 3 4 5 6 7 8 9 10
4. **Has your appetite changed in the last month?**
Better Worse
Stable Don't know
5. **When during the day do you feel that your appetite is worse?**
Morning Noon Evening Don't know
6. **Do you ever get hungry?**
Never Sometimes Most of the time
7. **What do you do if you are hungry?**
Eat Sometimes eat Cannot eat Don't eat Other
8. **Has the amount you eat changed in the last month?**
Increased Stable Decreased Don't know
9. **Did your weight change since you became ill?**
Yes No Don't know
If yes, has it?
increased? _____lb decreased? _____lb
10. **Did your weight change over the last month?**

performance status, characteristics of weight loss, or number of other GI symptoms. By multivariate regression analysis, performance status (ECOG score) inversely correlated ($r=0.4$) with the NRS score. The NRS was also found to be inversely correlated ($r=0.6$) with the categorical scale anorexia severity ($p<0.001$ ANOVA; $p<0.001$ Jonckheere–Terpstra; Fig. 4).

Diurnal appetite variation

Twenty-four percent (22/95) had worse appetite at night.

Weight loss

Seventy-nine percent (89/95) had some degree of weight loss; the majority (72%) of those with any weight loss had lost >5% of pre-cancer body weight. Amongst those with documented severity of weight loss, 65% had lost $\geq 10\%$. Severity of weight loss (≥ 5 ; $\geq 10\%$) did not influence the prevalence of gastrointestinal symptoms; the two weight loss groups were comparable in age, gender, and performance status. Median weight loss in the prior month was 10 lbs (range 2–60). Only 38% appeared clinically cachectic.

Fig. 1 (continued)

- Yes No Don't know
- If yes, has it?
- increased? _____lb decreased? _____lb
11. **How much did you weigh before you became ill?** _____lbs.
12. **Observer only: Does the patient appear clinically cachectic?** Yes No
13. **Did you have any of the following symptoms during the last month?**
- | | | |
|---|------------------------------|-----------------------------|
| Hiccups | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Feeling full after a few bites of food? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Nausea | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Vomiting | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Belching | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Indigestion | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Abdominal pain | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Bloating | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Constipation | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Do you think your appetite is reduced because of this | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

Food aversions

Food aversions were present in 57% (52/90). Prevalence correlated with more severe anorexia ($p < 0.001$) and the presence of early satiety ($p < 0.001$) and taste changes ($p = 0.04$). Forty-four percent of those with food aversions reported that they avoided meat (chicken, beef, and fish), while 37% avoided coffee, pasta, bread, and vegetables, 19% desserts and sweet foods. There was no association between food aversions and age, gender, tumor primary site, chemotherapy, or radiation therapy.

Taste and smell

Sixty-nine percent (65/95) reported taste changes, the prevalence of which correlated with older age ($p = 0.003$). Two thirds of these involved combinations of altered sense of sweet, salt, bitter, and sour. In the remainder, specific subjective taste changes were evenly distributed between sweet (10%), bitter (4%), salt (3%), and sour (2%). Forty-two percent (40/95) noted changes in the smell of food. There was no association between taste changes and gender, primary site, chemotherapy, or radiation.

Fig. 1 (continued)

14. **Are there particular foods that you used to like but now don't?**
Yes No Which kind of food: _____
15. **Changes in smell?** Yes No
16. **Taste changes?** Yes No
 If yes, too bitter too sour too sweet too salty None of these
17. **Did your appetite change with chemotherapy?** Yes No N/A
18. **Did your appetite change with radiation?** Yes No N/A
19. **Does it bother you that your appetite is reduced?** Yes No

Females only:

1. **Have you had any of the following during your menstrual period and/or pregnancy?**
- A. Decreased appetite? Yes No Don't know
- B. Feel full after eating a few bites? Yes No Don't know
- C. Nausea or vomiting? Yes No Don't know
- D. Food preference changes? Yes No Don't know
- E. Taste changes? Yes No Don't know
- F. If yes to above, which food seemed? Bitter Sour Sweet Salty
2. **Is there anything else you want to tell me about your appetite that we have not covered?**

Influence of gender

Nausea ($p=0.01$) and vomiting ($p=0.03$) were more frequent in females. There was in men a (non-statistically significant) trend for constipation, abdominal pain, and hiccups to occur more often than in women.

Effects of chemotherapy and/or radiation

Forty-two percent (40/95) had received chemotherapy, 55% (22/40) within a month of the survey. Of the latter, 59% (13/22) had severe anorexia. The majority, 93% (37/40),

attributed their anorexia to chemotherapy. Twenty-two percent (21/95) had undergone radiation, 48% (10/21) within a month of the survey. Of the latter, 70% (7/10) had severe anorexia. Most [90% (19/21)] treated with radiation attributed their appetite loss to radiation. Anorexia severity by NRS did not differ between those given chemotherapy or radiation recently and those who had not.

Gastrointestinal symptoms during pregnancy and menstrual periods

There was no relationship with cancer anorexia.

Table 1 Demographic characteristics (N=95)

Variable	Number (N)	Percentage
Gender (F/M)	49/46	52/48
Age (mean ± SC)	63±13	
Race		
White	66	69
African-American	22	23
Hispanic	0	0
Other	2	2
Unknown	5	5
Performance status (ECOG)		
0	6	6
1	35	37
2	23	24
3	26	27
4	5	5
Primary cancer diagnosis		
Lung Cancer	25	26
Gastrointestinal/Pancreatic	23	24
Breast	9	9
Others	38	40

Discussion

We examined the GI symptom profile in cancer anorexia to determine the total contribution of various GI symptoms to the ACS. Anorexia may be conceived of as an isolated symptom (perhaps suggesting a centrally mediated etiology due to hypothalamic dysfunction) or perhaps part of a more complex symptom cluster that includes other gastrointestinal symptoms (which might reflect peripheral dysfunction).

Patient demographics in this study resembled those from our previous symptom studies [20, 21, 28, 37, 42, 45]. Hence, we believe that this survey generally represents the experience of patients with advanced cancer. The patients in the study represent approximately 10% of all patients referred to the palliative medicine program during that time frame. Anorexia was a persistent problem, typically chronic and often moderate to severe. The NRS has a high (inverse) correlation with the patient self-assessed grade of anorexia

on a categorical scale. This supports the use of an NRS in both screening for anorexia and as a severity measure of anorexia.

Anorexia was more severe in those with the greatest weight loss. Anorexia was not absolute; most people became hungry sometimes [43]. Appetite was worse in the evening for about a quarter of those with significant anorexia. These abnormal diurnal appetite patterns did not correlate with anorexia severity. Awareness of these changes should help counseling and management. Appetite is known to be influenced by circadian rhythms, and normally, more food is eaten later as satiety diminishes during the day [14, 15]. Changes in meal size and frequency are described in several animal tumor models [13, 25].

A cachectic appearance was not typical. Body mass index can be normal, yet significant weight loss may have occurred due to premonitory obesity [42]. Weight loss in cancer is common and predicts shorter survival [18, 31, 42]. Severe weight loss correlates with the total number of GI symptoms [28] and anorexia [36, 37]. Multiple GI symptoms occur in most people with moderate or severe cancer anorexia [28, 37, 42]. We found no relationship between severity of reported weight loss, and individual GI symptoms. The absence of clinical cachexia in a patient complaining of anorexia may dissuade physicians from intervening, even though it is noteworthy that most complained that their anorexia was significant in nature and some weight loss was nearly universal.

The importance of early satiety has been previously reported by our group [20, 42]. The mechanism is unknown [15, 37]. It reduces food intake and predicts shorter survival [18, 34]. Early satiety can occur without anorexia, but it is experienced by most with moderate to severe anorexia [14, 18, 20, 31, 43]. Early satiety is unrelated to primary site, chemotherapy, or radiation therapy. A significant relationship exists between early satiety and GI dysmotility [37]. Paradoxically, those with early satiety complain of anorexia, yet also become hungry when fasted [43]. Persons with both anorexia and early satiety may have mood changes absent in those with anorexia without early satiety [43]. This may indicate that there is a central

Fig. 2 Anorexia: early satiety, taste changes, and food aversions (N=95)

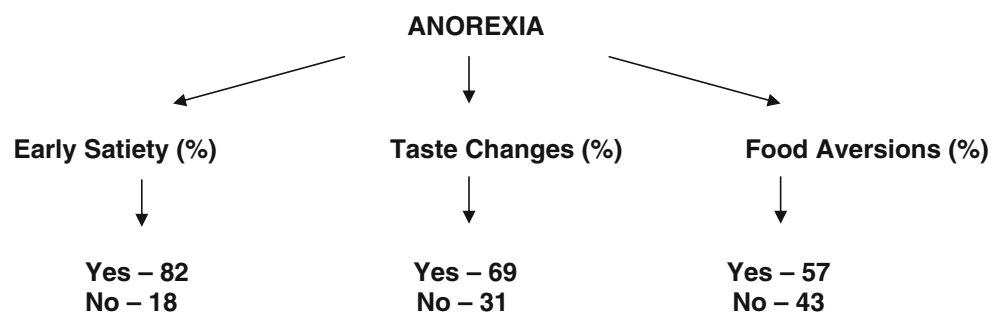
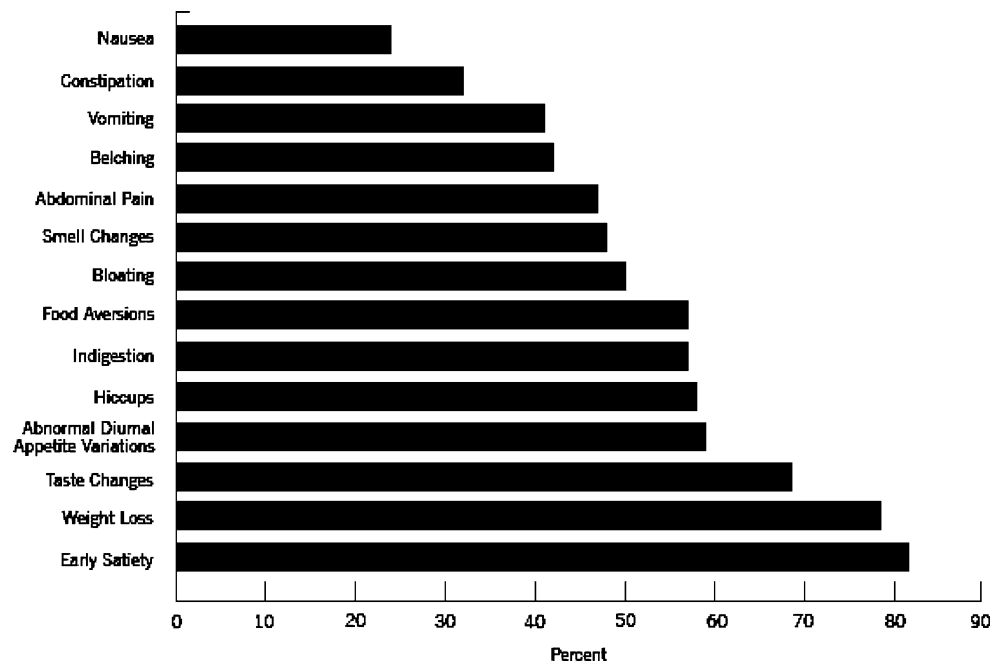


Fig. 3 Gastrointestinal symptom prevalence in cancer anorexia ($N=95$)



mechanism to early satiety, which is traditionally considered to arise from altered GI motility [40, 44].

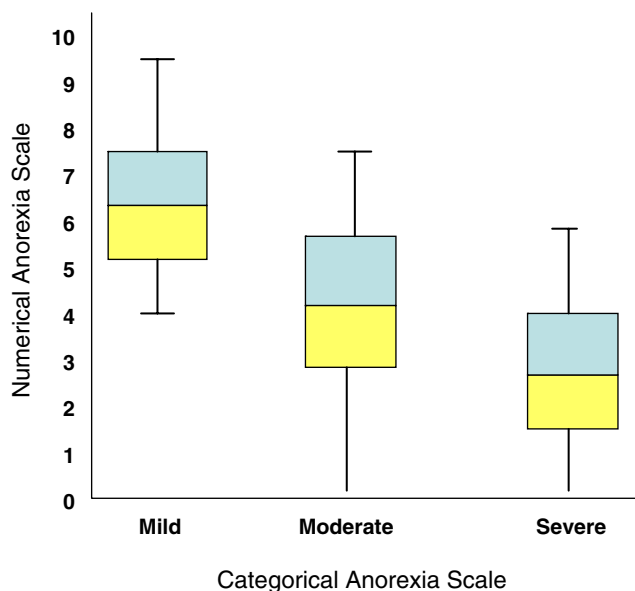
We observed both food aversions and taste changes in most with anorexia. Those with food aversions were also more likely to have early satiety. Both food aversions and taste changes may occur more frequently as anorexia worsens [17, 24, 27, 38]. Some suggest that such aversions are psychologically conditioned by cancer treatment [17, 32]. Clinical management of cancer anorexia may be complicated

by both early satiety (which will limit food volume) and food aversions (which limit the type of food).

Taste changes (but not surprisingly food aversions) were more common with older age. Subjective taste changes were usually non-specific but, when identified, were equally distributed between bitter, salt, sour, and sweet. Others have reported increased subjective taste thresholds for sweet taste and reduced thresholds for bitter sensation in cancer illness or from anti-tumor treatment [10, 19]. These reports have not been objectively confirmed. Aging itself alters taste and reduces food preferences and variety (even before a cancer diagnosis) [11, 41]. Greater taste changes in the elderly person with cancer can therefore be anticipated.

A sizeable minority of those interviewed had gotten recent chemo- or radiation therapy. The majority believed it had affected their anorexia. Anti-tumor therapy may worsen preexisting cancer anorexia and perhaps cause taste changes even after treatment is completed [5, 33]. Chemotherapy temporarily reduces taste sensation [4, 32, 33]. Anorexia may in some be due to taste changes induced by chemotherapy and radiation [2, 5, 32, 33]. Unlike anorexia, we did not find any association between food aversions or taste changes and anti-tumor therapy, suggesting that the cancer itself causes food aversions and taste changes independent of chemo- or radiation therapy. These observations must be treated with caution because of the varying intervals between anti-tumor treatment and the survey.

Females in this study experienced more nausea and vomiting, which confirms our previous reports [20–22]. These observations need to be considered when interpreting symptom profiles in cancer patients. Anorexia, early satiety, altered taste, food aversions, and diurnal appetite variations



$p < 0.001$ ANOVA; $p < 0.001$ Jonckheere-Terpstra

Fig. 4 Anorexia numerical and categorical scales correlation

are common during the normal menstrual cycle or pregnancy [6, 7, 39]. We sought but did not find any relationship between past menstrual and pregnancy-related appetite changes and the current GI symptoms of cancer anorexia. Recall obviously may have been a problem and the numbers too small to adequately draw conclusions.

The definition and assessment of cancer anorexia is problematic, as it is truly a syndrome as illustrated by this study. Most did become hungry sometimes despite complaining of anorexia. Most validated symptom assessment tools have only a single question regarding anorexia. They therefore inadequately assess the extent of this problem. They do not assess early satiety or other common concurrent GI symptoms, taste changes, food aversions, and diurnal appetite. They underestimate the full anorexia experience and fail to provide a true picture of the nature of cancer anorexia.

Anorexia can be variously perceived by patients as early satiety, reduced total food intake, lack of hunger, altered taste and/or smell, limited food preference, infrequent eating, or an altered circadian eating habit. Early satiety, chronic nausea, and food aversions are all appetite-related sensations (and perhaps also misinterpreted as anorexia by some clinicians), but are different experiences as related by patients. Usual descriptors used in some questionnaires such as lack of hunger or a sense of fullness do not necessarily measure the same perception [1, 35, 41].

It is important to reassess the value of validated anorexia questionnaires given this information. A comprehensive questionnaire, we suggest, should include multiple associated symptoms found in the cancer anorexia syndrome to truly understand what patients mean by anorexia. This could also help us understand the benefits of drugs intended as appetite stimulants on the entire spectrum of the syndrome. Most studies of appetite stimulants in cancer have not included the commonly associated GI symptoms we have identified as either primary or secondary outcome measures [47, 48]. Management of anorexia must include these other GI symptoms. This is particularly so given that many patients believed they contributed to (not just accompanied) the anorexia. Appetite stimulants alone may theoretically worsen early satiety as intake increases from the stimulant, but perhaps accompanied by volume limitations from the satiety. Food aversions might theoretically improve with appetite stimulants that work (presumably) centrally, while peripheral acting promotility medications may improve early satiety.

There were several limitations to this study. Consecutive patients were not surveyed (as was our original intent). However, the cohort was consistent with our patient demographics from previous symptom studies such that we believe the results are generalizable to advanced cancer. Information about medications was not collected. Psycho-

logical distress, primary cancer site, advanced cancer stage, and treatment morbidity may influence anorexia [19]. We did not screen for psychological stress, but we did not find that anti-tumor treatment or primary site influenced anorexia severity. We used a symptom checklist rather than a validated anorexia assessment tool. We believe that it is impossible (with the available validated tools) to adequately study the complex symptomatology of anorexia. The same survey should perhaps be repeated in cancer patients without anorexia. Future research should examine the development of a comprehensive validated anorexia questionnaire.

Conclusions

Anorexia is part of a complex syndrome. Multiple complex GI symptoms typically occur in association with cancer-related anorexia; it uncommonly occurs alone. Anorexia was most severe in those with the greatest weight loss. Almost all with significant anorexia had multiple other GI symptoms. Weight loss was very common, but clinical cachexia present only in a minority. Early satiety, taste changes, food aversions, nausea, abnormal diurnal appetite patterns, constipation, and vomiting occurred frequently. Severe anorexia correlated with poor performance status, and the presence of food aversions. Changes in the normal diurnal appetite variation were common. Most of those with anorexia did become hungry sometimes, often earlier in the day. Taste changes were non-specific in most of those affected and increased in prevalence with older age, but prevalence was unaffected by anorexia severity. Recent chemotherapy or radiation therapy appeared to influence anorexia. Primary tumor site did not seem to influence anorexia severity. Gender affected the GI symptom profile, with anorexic females experiencing more nausea and vomiting. A numerical rating scale appears a practical alternative to screen for presence and severity of anorexia. Systematic assessment of these symptom profiles should help improve understanding of the pathophysiology and clinical features of the anorexia–cachexia syndrome, help develop better outcome measures for clinical research, and lead to better therapy.

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