Support Care Cancer (2013) 21:735–748
DOI 10.1007/s00520-012-1574-9

ORIGINAL ARTICLE

Nausea still the poor relation in antiemetic therapy? The impact on cancer patients' quality of life and psychological adjustment of nausea, vomiting and appetite loss, individually and concurrently as part of a symptom cluster

Carlo Pirri · Evan Bayliss · James Trotter · Ian N. Olver · Paul Katris · Peter Drummond · Robert Bennett

Received: 27 March 2012 / Accepted: 13 August 2012 / Published online: 14 September 2012

Abstract
Purpose Despite significant antiemetic advances, almost 50 % of treated cancer patients still experience nausea and vomiting (N&V). The goal of antiemetic therapy—complete prevention of treatment-induced nausea and/or vomiting (TIN+/−V)—remains elusive for several reasons. Potentially, N&V may be part of a symptom cluster where co-occurring symptoms negatively affect antiemetic management. Consequently, we examined TIN+/−V incidence and the impact of nausea, vomiting and symptom cluster(s) containing them, respectively, on patients' quality of life (QoL) and psychological adjustment across treatment.
Methods A longitudinal secondary analysis was performed on data from a prospective, observational QoL study involving 200 newly diagnosed cancer patients who underwent combined modality treatment. QoL, psychological adjustment and patient/clinical characteristics were examined at pretreatment, on-treatment (8 weeks) and post-treatment.
Results Overall, 62 % of patients experienced TIN+/−V, with TIN (60 %) doubling TIV incidence (27 %). Exploratory factor analyses of QoL scores at each treatment time point identified a recurrent gastrointestinal symptom cluster comprising nausea, vomiting and appetite loss. Approximately two thirds of patients reported co-occurrence of all three symptoms, which exerted synergistic effects of multiplicative proportions on overall QoL. Patients who reported co-occurrence of these symptoms during treatment experienced significantly greater QoL impairment (physical, role and social functioning, fatigue, N&V, appetite loss, overall physical health, overall QOL) and psychological distress (cancer distress, premorbid neuroticism) than those unaffected ($0.001 > p \leq 0.05$). Moreover, nausea was more pervasive than vomiting or appetite loss across treatment and had a greater impact on overall QoL. While antiemetic therapy was effective for vomiting and helped prevent/relieve associated appetite loss, the benefits for appetite loss were seemingly constrained by its failure to exert adequate control over nausea in many patients.
Conclusions TIN+/−V still represents a very major concern for patients. Uncontrolled TIN+/−V often results in significant appetite and weight loss, leading to increased risk for malnutrition. Malnutrition and weight loss, in turn, are associated with poorer prognosis, treatment tolerance and

Electronic supplementary material The online version of this article (doi:10.1007/s00520-012-1574-9) contains supplementary material, which is available to authorized users.

C. Pirri (✉) · P. Drummond · R. Bennett
Faculty of Health Sciences, Murdoch University,
90 South Street,
Murdoch, WA 6150, Australia
e-mail: cpirri@gmail.com

E. Bayliss
Department of Medical Oncology, Royal Perth Hospital,
Perth, Australia

J. Trotter
Medicine and Pharmacology Royal Perth Hospital Unit,
University of Western Australia,
Crawley, Australia

I. N. Olver
Cancer Council Australia,
Sydney, Australia

I. N. Olver
Discipline and School of Medicine, University of Adelaide,
Adelaide, Australia

P. Katris
Western Australian Clinical Oncology Group,
West Perth, Australia

response, performance status, QoL and survival. Consequently, a multiple symptom intervention approach focusing on N&V as core symptoms is recommended. Clinicians should genuinely consider combining essential antiemetic therapies with other evidence-based pharmacological (e.g. nausea: psychotropics, such as olanzapine) and non-pharmacological approaches (e.g. N&V: relaxation) in attempts to not only improve prevention and control of N&V for their patients, but also reduce the synergistic impact of cluster symptoms (e.g. N&V, appetite loss) as a whole and resultant QoL impairment likewise. Where associated symptoms are not adequately controlled by these antiemetic-based interventions, targeted evidence-based strategies should be supplemented.

Keywords Nausea · Vomiting · Chemotherapy · Cancer · Symptom cluster · Quality of life · Psychological · Anorexia · Radiotherapy · Surgery · Non-pharmacological

Introduction

Despite dramatic improvements in antiemetic control conferred by serotonin (5-HT_3) and neurokinin (NK-1) receptor antagonists and prescriptive antiemetic guidelines, approximately 50 % of cancer patients still experience nausea and vomiting (N&V) during treatment, with nausea proving to be more pervasive than vomiting (incidence: 37–70 vs. 13–34 %) [1–3]. Several patient, clinical and quality of life (QoL) factors associated with the development of N&V during treatment have been identified [3–6], the most important being the emetogenic potential of chemotherapy received [7]. Other factors include female gender [3–5], younger age [4–6], a history of N&V [5] or low alcohol consumption [4], preexisting anxiety [5, 6], a high expectation of developing N&V after chemotherapy [4, 5], emetogenic potential of radiotherapy [7] and undergoing surgery [4–6] or combined therapy [7].

Uncontrolled treatment-induced nausea and/or vomiting (TIN+/−V) due to chemotherapy, radiotherapy and/or surgery results in a range of physical and psychosocial symptoms, which impact considerably on patients' QoL and healthcare costs [2, 3, 6, 8–11]. Nevertheless, few prospective studies have quantitatively demonstrated that aspects other than physical functioning are adversely affected by uncontrolled TIN+/−V [8, 12]. Moreover, studies examining TIN+/−V have commonly assessed the impact of chemotherapy-induced nausea and vomiting (CINV) per se on QoL, and have done so using the Functional Living Index–Emesis (FLIE) questionnaire [8–10, 13]. Unfortunately, the FLIE has some limitations, most notably, the use of aggregate scores that may lack sensitivity to detect differences within and across individual QoL domains, a relative lack of published psychometric evaluation and the omission of concomitant symptoms that patients may experience (e.g. fatigue) [14, 15]. Patients most at risk of TIN+/−V include those who have received previous chemotherapy, are planned for concurrent chemoradiation or have poor performance status. Most TIN+/−V studies have been RCTs which have often excluded these groups; thus, TIN+/−V outcomes from these trials cannot be generalised [2–4, 8, 10].

Current evidence-based antiemetic guidelines (e.g. Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) [7], American Society of Clinical Oncology [16], National Comprehensive Cancer Network) [17] maintain that the goal of antiemetic therapy is complete N&V prevention. The inability, thus far, to achieve a desirable level of control for all patients is multifactorial. Reasons include the predominating failure to control nausea, continued use of emetogenic chemotherapy regimens, incomplete understanding of the mechanisms underlying TIN+/−V, underestimation of TIN+/−V incidence, lack of compliance with antiemetic guidelines, infrequent/inadequate assessment of TIN+/−V and its risk factors in routine clinical practice, antiemetic development targeting vomiting at the expense of nausea and previous studies examining TIN+/−V within the constraints of clinical trials [18, 19].

Another reason, albeit little-considered, is that N&V may be part of a more extensive *symptom cluster*, a concept which has only recently become prominent in cancer QoL research. Symptom clusters are defined as follows:

> "A symptom cluster comprises 2 or more symptoms that are related to each other and that occur together. Symptom clusters are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms. Relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters. Symptoms in a cluster may or may not share the same etiology." [20] (p. 278)

Symptom clustering may be therapeutically important for TIN+/−V because treatment of nausea or vomiting may be affected or influenced by other symptoms occurring in a cluster with them (e.g. bloating, difficulty swallowing) [21, 22].

The goals of the present study were to assess the "real-world" incidence of TIN+/−V (i.e. acute N&V developing within 24 h of treatment + delayed N&V developing more than 24 h, up to several days, after treatment) [7] in cancer patients receiving combined modality treatment in a routine clinical setting; identify the presence and composition of any symptom cluster(s) involving N&V over time at the onset, during and at the end of treatment; and, most importantly, examine the impact of nausea, vomiting and any

symptom clusters containing them, respectively, on the QoL and psychological adjustment of patients across combined treatment.

Materials and methods

A secondary analysis of data collected from a prospective, longitudinal, observational design involving a heterogeneous group of 200 cancer patients was performed. The ethics committees of the participating institutions approved the study. All patients provided written and informed consent.

Patients

Participants were recruited for a larger study evaluating QoL and psychosocial distress from a consecutive series of 287 eligible medical oncology outpatients, who largely received combined treatment (including chemotherapy) at Royal Perth Hospital, Western Australia, between 1997 and 2003. In the week before treatment began, patients were approached and given a verbal explanation of the study plus an information sheet.

Eligibility criteria

Eligibility criteria included histological confirmation of cancer, age of 18 years and above, absence of acute psychiatric symptoms or conditions that could cause emesis (i.e. central nervous system/head and neck metastasis, (ongoing) gastrointestinal obstruction, a history of motion sickness or alcohol/drug abuse, pregnancy, metabolic/electrolyte imbalances, pain conditions treated with non-stable doses of opioids and any other uncontrolled medical condition that may cause nausea and vomiting, such as increased intracranial pressure or hypercalcaemia; see Table 1 footnote), no prior cancer treatment for the current diagnosis (excluding surgery) and adequate English literacy and cognitive ability to complete the study questionnaires.

Data collection

Data concerning demographics, clinical characteristics and potential risk factors for TIN+/−V were collected from patients, oncologists and medical records. Questionnaires were completed by patients at pretreatment (within 7 days of the start of chemotherapy ± radiotherapy), on-treatment (8 weeks±1 week), post-treatment (within 7 days of the last treatment received) and follow-up (6 months). As this study was specifically aimed at assessing TIN+/−V (acute + delayed N&V) and associated symptom clusters in patients during treatment, follow-up data were excluded from

Table 1 Patient and clinical characteristics of the sample (N=200)

Patient/clinical characteristics	Number of patients, n (%)
Sex	
Male	95 (47.5)
Female	105 (52.5)
Marital status	
Married/defacto	140 (70.0)
Divorced/separated/widowed	45 (22.5)
Single, never married	15 (7.5)
Employment status[a]	
Actively employed/working	29 (14.6)
Not actively employed/working	169 (85.4)
Health insurance status	
Public	171 (85.5)
Private	29 (14.5)
Alcohol misuse history	
No prior history	196 (98.0)
Previous history	4 (2.0)
Cancer history	
No prior history	151 (75.5)
Previous history	49 (24.5)
Primary diagnosis[b]	
Breast	58 (29.0)
Colorectal	56 (28.0)
Other	86 (43.0)
ECOG performance status[a]	
0 (fully active)	53 (62.4)
1–4 (not fully active)	32 (37.6)
Treatment received	
Chemoradiation + surgery	53 (26.5)
Chemotherapy + surgery	66 (33.0)
Chemoradiation	35 (17.5)
Chemotherapy only	46 (23.0)
Cancer-related procedures[c]	
Single procedure	82 (61.6)
Multiple procedures	51 (38.4)
Cancer resection	
No	81 (40.5)
Yes	119 (59.5)
Previous chemotherapy experience	
No	161 (80.5)
Yes	39 (19.5)
Chemotherapy agents received[a]	
Fluorouracil	114 (64.0)
Cyclophosphamide	54 (30.3)
Leucovorin	45 (25.3)
Methotrexate	36 (20.2)
Cisplatin	31 (17.4)
Epirubicin	26 (14.6)
Other	59 (33.2)
Radiotherapy	
No	112 (56.0)
Yes	88 (44.0)
Radiotherapy courses received	
Single course (or part thereof)	81 (92.0)
Multiple courses	7 (8.0)

Table 1 (continued)

Patient/clinical characteristics	Number of patients, *n* (%)
Radiotherapy emetogenicity[a]	
Minimal/low	63 (88.7)
Moderate/high	8 (11.3)
Age	
18–49 years	62 (31.0)
50 years and over	138 (69.0)
Education[a]	
Primary	20 (10.2)
Secondary	91 (46.7)
Tertiary	84 (43.1)
Residence[a]	
Metropolitan	169 (84.9)
Rural	30 (15.1)
Psychiatric history[a]	
No prior history	171 (88.1)
Previous history	23 (11.9)
Comorbid medical history[a]	
None/single condition	108 (56.0)
Multiple conditions	86 (44.0)
Recurrence	
No	169 (84.5)
Yes	31 (15.5)
Disease status	
Localised disease	19 (9.5)
Locally advanced	109 (54.5)
Metastatic	72 (36.0)
Treatment intent	
Curative	23 (11.5)
Adjuvant/neoadjuvant	102 (51.0)
Palliative	75 (37.5)
Treatment duration[a, d]	
0–3 months	63 (33.7)
3–6 months	76 (40.6)
>6 months	48 (25.7)
Surgery type	
Breast	49 (37.1)
Colorectal	44 (33.3)
Other	39 (29.6)
Surgery prior to adjuvant chemoradiation	
No	94 (47.0)
Yes	106 (53.0)
Chemotherapy courses received	
Single course (or part thereof)	181 (90.5)
Multiple courses	19 (9.5)
Chemotherapy emetogenicity	
Minimal/low	98 (49.0)
Moderate/high	102 (51.0)
Antiemetics administered[e]	
No	43 (21.5)
Yes	157 (78.5)
Concurrent chemoradiation	
No	154 (77.0)
Yes	46 (23.0)
Radiotherapy site[a]	
Breast/axilla	22 (28.2)
Chest/supraclavicular	15 (19.2)
Pelvis	10 (12.8)
Other	31 (39.8)

Patients were predominantly Caucasian (84 %). Of 87 potential study patients initially excluded, seven had conditions (head and neck/central nervous system metastasis, uncontrolled chronic pain, chronic metabolic disorders, pregnancy) that may have caused emesis and the remainder declined study participation. Of a further 47 patients excluded during treatment, 15 were due to changes in medical care (treatment transferred to another hospital, clinic discharge, patients did not attend clinic appointments or ceased clinical contact) and 15 were due to study withdrawal (five physically unwell, two emotionally distressed, eight with reasons unrelated to cancer). One physically unwell patient withdrew due to uncontrolled nausea and abdominal pain while receiving highly emetogenic chemotherapy for colorectal cancer

[a] Patient numbers do not always equal to total sample/subgroup size due to missing data

[b] Primary diagnoses included 79 abdominal and 16 pelvic malignancies

[c] Cancer-related procedures include cancer resections plus related procedures (e.g. colostomy/ileostomy, infusaport insertion)

[d] Treatment duration excludes any surgery prior to adjuvant chemoradiation received before medical oncology presentation

[e] All patients who were not prescribed antiemetics received minimally/low emetogenic treatment and antiemetic therapy consistent with guidelines in force at the time and place of the study, which predated the NK-1 antagonists

analysis. Data from patients not completing questionnaires within the specified intervals were also excluded.

The on- and post-treatment assessment, in each instance, occurred at 7 days following the end of a treatment cycle to capture both acute and delayed N&V (i.e. TIN+/−V incidence), as well as other treatment effects. Also, the on-treatment assessment was performed at 8 weeks (± 1 week), chiefly to minimise patient burden associated with more frequent or ongoing assessment (e.g. patient diaries) that would have added to the more extensive battery of questionnaires (100 items) employed in the larger QoL study. Moreover, it was considered an optimal time point to measure the incidence of acute and delayed N&V (and other side effects) during treatment, as it coincided with the administration of chemotherapy (undertaken by all patients, unlike radiotherapy and surgery) that was generally given weekly or every 3–4 weeks for a period of 3–12 months.

Questionnaires

Patients were administered standardised questionnaires assessing QoL and psychological distress, which have

been described in detail previously [23]. They included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) V2.0 [24, 25], Selby Quality of Life (QoL) Uniscale (overall QoL) [26], Physical Health (PH) Uniscale (overall physical health) [24, 26], Beck Depression Inventory Short Form (BDI-SF; clinical depression) [27], Impact of Event Scale-Intrusion Subscale (IES-IS; cognitive–emotional distress related to cancer) [28] and Eysenck Personality Questionnaire-Revised (EPQ-R)—Neuroticism Short Form (SF) (premorbid neuroticism at pretreatment only) [29]. The EORTC QLQ-C30 assessed the study's primary endpoint for N&V, defined in the present study as the absence of total control (i.e. no nausea, vomiting or retching and no rescue medication).

Statistical analysis

Exploratory factor analysis (EFA) in the form of principal components analysis, using both oblique and orthogonal rotations, was performed on QoL (EORTC QLQ-C30, Selby QoL Uniscale, PH Uniscale) at each treatment time point to identify any symptom cluster (factor) containing nausea and/or vomiting. Criteria to determine the best factor model included: (a) exclusion of items exhibiting Kaiser's measurement of sampling adequacy, Kaiser–Meyer–Olkin or communality values <0.5, (b) Bartlett's test of sphericity being significant ($p<0.0001$), (c) retention of factors with eigenvalues > 1 that were supported by scree plot analysis and clinical/theoretical plausibility of factors, (d) factor loadings ≥0.4 for interpretation of factors (explaining ≥16 % of total variance), (e) Cronbach's alpha ≥0.7 for each factor and (f) stability of factor solutions across analyses employing oblique and orthogonal rotations [30, 31]. Stability or persistence of the symptom cluster (factor) containing nausea and/or vomiting across treatment time points was also established quantitatively by the criterion that at least 75 % of symptoms in the initial cluster (pretreatment) must be present in subsequent clusters (on- and post-treatment) [31].

The impact on QoL domain scores and psychological functioning of any TIN+/−V symptom cluster identified and its individual symptoms was examined across treatment (pre-, on- and post-treatment) via univariate analyses using split-plot analyses of covariance. Additionally, the impact on overall QoL of any TIN+/−V symptom cluster identified was assessed at: (a) each treatment time point via multivariate analyses using hierarchical multiple regression ($p\leq0.1$ for retention of predictor variables in each regression model) and (b) across treatment using a multiple regression model with repeated measures (linear mixed model analysis, LMM), with the added ability to retain patients in the analysis who have missing data across one or more treatment time points [30, 32]. The level of significance for all analyses was set at $p\leq0.05$.

Results

Patient characteristics

Two hundred (70 %) of the eligible patients consented and completed baseline questionnaires. Of these, 178 (89 %) patients advanced to on-treatment (8 weeks±1 week) and 153 (76 %) progressed to post-treatment. During treatment, 47 patients were withdrawn due to death (15), changes in medical care (15), patient withdrawal (15) and loss to follow-up (two).

Patient and clinical characteristics have been described in detail previously [23] and are summarised in Table 1; they are typical of Western Australian cancer patients at the time of the study [33]. Briefly, all patients received chemotherapy; 161 (80 %) were chemotherapy-naïve. Overall, 239 chemotherapy regimens were administered (range of cycles: 2–12); fluorouracil + leucovorin (FU/LV, 19 %) and cyclophosphamide + methotrexate + FU (CMF, 11 %) were most prevalent. According to the MASCC/ESMO antiemetic guidelines [7], 102 (51 %) patients received moderately/highly emetogenic chemotherapy (M/HEC; ≥30 % emetic risk without prophylaxis), and the remaining 98 (49 %) received minimally/low emetogenic chemotherapy (M/LEC; <30 % emetic risk without prophylaxis).

Antiemetic therapy consistent with guidelines in force at the time and place of the study was used for most patients (this predated the NK-1 antagonists). Overall, 130 (65 %) patients received 5-HT_3 receptor antagonists (e.g. ondansetron) + corticosteroids (e.g. dexamethasone), 55 (28 %) were prescribed dopamine receptor antagonists (e.g. metoclopramide) and 43 (22 %) patients received no antiemetics.

Prevalence/incidence, persistence and severity of TIN+/−V

Overall, TIN+/−V was experienced by 123 (62 %) patients, TIN only by 70 (35 %) patients, TIV only by four (2 %) patients and concurrent TIN+/−V by 50 (25 %) patients. Thus, TIN occurred in 120 (60 %) patients and TIV in 54 (27 %) patients overall. At on-treatment (8 weeks), TINV was reported by 87 (49 %) patients, TIN only by 55 (31 %) patients, TIV only by four (2 %) patients and concurrent TINV by 28 (16 %) patients. Thus, TIN occurred in 83

(47 %) patients and TIV in 32 (18 %) patients at on-treatment (8 weeks). Finally, TINV was reported by 86 (56 %) patients, TIN only by 51 (33 %) patients, TIV only by three (2 %) patients and concurrent TINV by 32 (21 %) patients at post-treatment. Thus, TIN occurred in 83 (54 %) patients and TIV in 35 (23 %) patients at post-treatment.

Impact of chemotherapy emetogenicity on patients' quality of life and psychological adjustment

No significant differences were found on any QoL or psychological dimension for patients treated with M/HEC (n=96) when compared to those who received M/LEC (n=57; $0.131 \leq p \leq 0.97$) after controlling for covariates (previous chemotherapy experience, surgery prior to adjuvant chemotherapy ± radiotherapy, variable treatment duration, antiemetic use, baseline QoL/psychological functioning score at pretreatment).

Identification of a TIN+/−V symptom cluster and its pattern across time during treatment

EFA was conducted on QoL scores at each treatment time point. Near-identical factor solutions were produced by orthogonal (varimax) and oblique (oblimin) rotations; thus, results of the latter are reported only (Table 2). At pretreatment, a six-factor solution explaining 68.2 % of the total variance in QoL was extracted. Of this variance, 7.2 % (approximately one tenth) was accounted for by a gastrointestinal (GI) symptom cluster consisting exclusively of nausea, vomiting and appetite loss. Similarly, a seven-factor solution emerged at both on-treatment and post-treatment, explaining 67.6 and 72.6 % of the total variance in QoL, respectively. Of the variance, 6.9 and 8.3 % (approximately one tenth) was accounted for by the same GI symptom cluster at on- and post-treatment, respectively. Cronbach's alpha for the GI cluster across treatment was 0.74, 0.73 and 0.73, respectively, indicating acceptable internal consistency. Consequently, all symptoms identified exclusively in the GI cluster (nausea, vomiting, appetite loss) at pretreatment were replicated at on- and post-treatment, thus establishing cluster stability across time during treatment.

Validation of the identified GI symptom cluster (nausea, vomiting and/or appetite loss)

It was hypothesised that previous chemotherapy experience coupled with higher scores (unweighted means) across symptoms would demonstrate clinical relevance of the GI symptom cluster. Indeed, patients with previous chemotherapy experience reported significantly greater GI symptom distress across time during treatment than those without (31.6 vs. 14.1, p=0.029) after controlling for covariates (surgery prior to adjuvant chemotherapy ± radiotherapy, variable treatment duration, baseline GI symptom distress scores at pretreatment).

Table 2 Gastrointestinal symptom cluster structure and symptom prevalence across treatment undertaken by a heterogeneous sample of cancer patients (N=200)

	Factor III (% prevalence)		
	Pretreatment	On treatment (8 weeks± 1 week)[a]	Post-treatment[b]
GI symptom cluster items			
Nausea	0.931 (14 %)	0.837 (48 %)	0.802 (54 %)
Vomiting	0.897 (2 %)	0.627 (18 %)	0.730 (23 %)
Appetite loss	0.488 (12 %)	0.448 (42 %)	0.533 (35 %)
GI symptom cluster prevalence[c]	20.5 %	61.8 %	63.8 %
Cronbach's alpha	0.74	0.73	0.73
Eigenvalue	3.44	2.82	3.14
Average communality	0.73	0.59	0.67
Variance in QoL explained by GI cluster	7.2 %	6.9 %	8.3 %
Total variance in QoL explained	68.2 %[d]	67.6 %[e]	72.6 %[e]
Nausea–vomiting intercorrelation	0.66***	0.39***	0.45***
Nausea–appetite loss intercorrelation	0.50***	0.39***	0.38***
Vomiting–appetite loss intercorrelation	0.38***	0.34***	0.32**

Gastrointestinal symptom cluster structure was determined via EFA of QoL measures (EORTC QLQ-C30, Selby QoL Uniscale, PH Uniscale) using an oblique (oblimin) rotation

GI gastrointestinal, *QoL* quality of life

**p<0.01; ***p<0.001

[a] n=178

[b] n=153

[c] GI symptom cluster incidence (overall)=71 %

[d] Total variance explained by a six-factor solution

[e] Total variance explained by a seven-factor solution

Impact on patients' quality of life and psychological adjustment of nausea, vomiting and appetite loss alone and as part of a GI symptom cluster

Patients with nausea experienced significantly greater QoL impairment/psychological distress overall across treatment (pre-, on-, post-treatment) than those unaffected in the areas of physical, role and social functioning, fatigue (39.6 vs. 31.0, p=0.003), appetite loss, overall physical health and overall QoL ($0.003 \leq p \leq 0.048$) after controlling for covariates. Results also approached significance (i.e. $p \approx 0.05$–0.06) for sleep disturbance (p=

0.056) and premorbid (pretreatment) neuroticism (EPQ-R Neuroticism SF; $p=0.052$). Comparably, patients with vomiting experienced significantly greater QoL impairment/psychological distress overall across treatment in physical, role and social functioning, fatigue, appetite loss, sleep disturbance, overall physical health and cancer distress (IES-IS; $0.001 \leq p \leq 0.034$) than those unaffected. Results approached significance for cognitive functioning ($p=0.062$) and overall QoL ($p=0.052$) also. Patients with appetite loss, however, experienced significantly greater QoL impairment overall across treatment in physical, role and social functioning, fatigue, nausea/vomiting and overall physical health ($0.001 \leq p \leq 0.049$) than those unaffected, while results approached significance for cognitive functioning ($p=0.054$) and sleep disturbance ($p=0.056$; Tables S1–S3 of the "Electronic supplementary material").

Turning to the impact of multiple symptoms, patients with nausea and/or vomiting experienced significantly greater QoL impairment/psychological distress overall across treatment in physical, role and social functioning, fatigue, premorbid neuroticism, overall physical health and overall QoL ($0.003 \leq p \leq 0.038$) than those unaffected after controlling for covariates (Table S4 of the "Electronic supplementary material"). More prominently, however, patients with GI cluster symptoms (nausea, vomiting and/or appetite loss) experienced significantly greater QoL impairment overall across treatment than those unaffected in physical, role and social functioning, fatigue, nausea/vomiting ($p<0.001$), appetite loss ($p<0.001$), overall physical health and overall QoL ($0.003 \leq p \leq 0.05$ otherwise) after controlling for covariates (Table 3). Results approached significance for cancer distress ($p=0.058$) also.

Impact of nausea, vomiting and appetite loss as part of a GI symptom cluster on patients' overall quality of life

Two-stage hierarchical multiple regression analysis examining the influence of the GI symptom cluster on patients' overall QoL at each treatment time point was performed (Table 4). Forced entry controlling for confounding variables or covariates (demographics; clinical characteristics, such as disease stage; pre-/on-treatment QoL) identified in previous studies and those inherent in the present study design (e.g. variable treatment duration) [7, 34, 35] plus stepwise elimination of exploratory predictors contained in the GI cluster (i.e. absence vs. presence of nausea, vomiting and appetite loss, respectively) was employed. At pretreatment, 12.0 % of the total variance in patients' overall QoL scores was explained by sex, age, preexisting comorbid conditions, prior cancer history, disease stage, time since diagnosis, previous chemotherapy experience, surgery prior to adjuvant chemotherapy ± radiotherapy (7.4 % cumulatively by confounding variables) and appetite loss (4.6 % alone). Age, disease stage and appetite loss ($0.003 \leq p \leq 0.043$) exhibited significant independent effects on overall QoL at pretreatment. After controlling for confounding variables, appetite loss accounted for a significant increase in explained variance of 4.6 % in overall QoL ($p=0.003$), while nausea and appetite loss individually did not significantly influence overall QoL at pretreatment ($p>0.1$) and were eliminated in the stepwise procedure.

At on-treatment, 32.3 % of the total variance in overall QoL was explained by confounding variables (27.7 % cumulatively) and vomiting (4.6 % alone). Age, preexisting comorbidities, previous chemotherapy experience, overall QoL at pretreatment and vomiting ($0.001 \leq p \leq 0.03$) exhibited significant independent effects on overall QoL at on-treatment. After controlling for confounding variables (including baseline QoL at pretreatment), vomiting accounted for a significant increase in explained variance of 4.6 % in the change in overall QoL ($p=0.021$), while nausea and appetite loss individually did not significantly influence overall QoL at on-treatment relative to pretreatment ($p>0.1$).

Finally, 47.7 % of the total variance in overall QoL at post-treatment was explained by confounding variables (41.9 % cumulatively) and nausea (5.8 % alone). Overall QoL at on-treatment ($p<0.001$) and nausea ($p=0.008$) exhibited significant independent effects on overall QoL at post-treatment. After controlling for confounding variables (including QoL at pretreatment and on-treatment), nausea accounted for a significant increase in explained variance of 5.8 % in overall QoL ($p=0.008$), while vomiting and appetite loss individually did not significantly influence overall QoL at post-treatment relative to pretreatment or on-treatment ($p>0.1$).

A LMM analysis (multiple regression with repeated measures) was performed to better examine the effect of GI cluster symptoms on overall QoL across time during treatment (Table 5). Controlling for other covariates (demographics, clinical characteristics), overall QoL impairment at the end of treatment (post-treatment) was significantly predicted by younger age ($p=0.028$), previous chemotherapy experience ($p=0.019$) and overall QoL impairment before treatment (pretreatment; $p<0.001$). Additionally, the co-occurrence of nausea, vomiting and appetite loss significantly predicted overall QoL impairment at the end of treatment (post-treatment; $p=0.002$, $b=-4.53$), and had a stronger synergistic impact than nausea + vomiting ($p=0.003$, $b=-3.62$), nausea + appetite loss ($p=0.004$, $b=-4.04$) or nausea alone ($p=0.002$, $b=-3.67$).

Table 3 Cancer patients' quality of life and psychological functioning across treatment in relation to nausea, vomiting and/or appetite loss as part of a gastrointestinal symptom cluster, after controlling for demographics, clinical variables and pretreatment (baseline) scores

	Pretreatment[a]	On-treatment (8 weeks±1 week)	Post-treatment	p[b]
Global quality of life: Selby QoL uniscale (patients)[c]—mean (SD)				
No GI cluster symptoms	6.9 (0.0)	6.4 (2.1)	7.7 (2.2)	0.009**
GI cluster symptoms	6.9 (0.0)	5.6 (2.0)	5.5 (2.1)	
Global health: Physical Health uniscale (patients)[c]—mean (SD)				
No GI cluster symptoms	7.2 (0.0)	7.3 (2.1)	8.2 (2.1)	0.004**
GI cluster symptoms	7.2 (0.0)	6.5 (2.0)	6.1 (2.1)	
Quality of life: EORTC QLQ-C30 functional scales[c]—mean (SD)				
Physical functioning				
No GI cluster symptoms	88.6 (0.0)	89.6 (23.9)	94.4 (25.1)	0.05*
GI cluster symptoms	88.6 (0.0)	82.1 (23.0)	78.4 (24.2)	
Role functioning				
No GI cluster symptoms	64.4 (0.0)	90.2 (28.5)	83.0 (29.8)	0.003**
GI cluster symptoms	64.4 (0.0)	63.5 (27.6)	67.0 (28.8)	
Emotional functioning				
No GI cluster symptoms	76.3 (0.0)	84.4 (17.0)	77.0 (20.8)	0.324
GI cluster symptoms	76.3 (0.0)	75.6 (16.2)	76.4 (19.8)	
Cognitive functioning				
No GI cluster symptoms	77.6 (0.0)	86.3 (16.6)	78.8 (16.9)	0.328
GI cluster symptoms	77.6 (0.0)	78.6 (16.1)	78.6 (16.3)	
Social functioning				
No GI cluster symptoms	75.6 (0.0)	86.2 (26.9)	88.3 (30.2)	0.009**
GI cluster symptoms	75.6 (0.0)	67.5 (25.8)	68.5 (29.0)	
Quality of life: EORTC QLQ-C30 symptom scales/single items[d]—mean (SD)				
Fatigue				
No GI cluster symptoms	29.2 (0.0)	24.2 (21.1)	24.6 (22.0)	<0.001***
GI cluster symptoms	29.2 (0.0)	41.7 (20.4)	45.9 (21.2)	
Nausea and vomiting				
No GI cluster symptoms	12.3 (0.0)	0.83 (23.1)	2.8 (25.0)	<0.001***
GI cluster symptoms	12.3 (0.0)	21.6 (22.4)	27.2 (26.2)	
Appetite loss				
No GI cluster symptoms	16.9 (0.0)	0.0 (0.0)	2.7 (32.4)	<0.001***
GI cluster symptoms	16.9 (0.0)	26.0 (25.7)	39.0 (31.3)	
Pain				
No GI cluster symptoms	27.7 (0.0)	18.6 (23.3)	29.7 (27.8)	0.526
GI cluster symptoms	27.7 (0.0)	20.1 (22.4)	21.1 (26.8)	
Sleep disturbance				
No GI cluster symptoms	38.3 (0.0)	28.0 (34.4)	37.3 (34.3)	0.892
GI cluster symptoms	38.3 (0.0)	33.2 (33.3)	34.4 (33.1)	
Depression: Beck Depression Inventory short form[d]—mean (SD)				
No GI cluster symptoms	2.6 (0.0)	2.1 (2.6)	2.3 (2.7)	0.377
GI cluster symptoms	2.6 (0.0)	2.7 (2.5)	2.9 (2.6)	
Cancer distress: Impact of Event Scale–Intrusion subscale[d]—mean (SD)				
No GI cluster symptoms	6.4 (0.0)	2.9 (5.5)	3.4 (4.7)	0.058
GI cluster symptoms	6.4 (0.0)	6.9 (5.4)	6.0 (4.6)	
Premorbid neuroticism: EPQ-R Neuroticism short form[d]—mean (SD)				
No GI cluster symptoms	2.3 (3.1)	–	–	0.033*
GI cluster symptoms	3.3 (3.0)	–	–	

Analyses involved 121 patients with GI symptoms and 32 patients without (n=153); 47 were off-study by post-treatment. Covariates: prior chemotherapy experience, surgery prior to adjuvant chemotherapy ± radiotherapy, variable treatment duration, chemotherapy emetogenicity, antiemetic use, baseline QoL/psychological functioning score

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

[a] Since pretreatment (baseline) score was a covariate in analyses, they are identical across the two groups for each domain

[b] Only p-values for between-subjects effects for GI symptom incidence in split-plot ANCOVAs are cited as within-subjects effects for treatment time point are secondary

[c] Higher scores=healthier functioning

[d] Higher scores=greater symptomatology/problems

Table 4 The impact of nausea, vomiting and appetite loss as part of a GI symptom cluster on patients' overall QoL scores at each treatment time point after controlling for demographics, clinical characteristics and overall QoL at pre-/on-treatment in hierarchical multiple regression analyses

Independent variable	Pretreatment[a] (*N*=200)					On-treatment[b] (8 weeks±1 week) (*n*=178)					Post-treatment[c] (*n*=153)				
	Step 1 (forced entry)		Step 2 (stepwise elimination)			Step 1 (forced entry)		Step 2 (stepwise elimination)			Step 1 (forced entry)		Step 2 (stepwise elimination)		
	B (SE)	*β*	B (SE)	*β*	*p*	B (SE)	*β*	B (SE)	*β*	*p*	B (SE)	*β*	B (SE)	*β*	*p*
Intercept/constant	7.19 (1.23)	–	6.93 (1.2)	–	<0.001***	0.7 (1.47)	–	0.57 (1.56)	–	0.716	4.52 (2.16)	–	5.06 (2.08)	–	0.018*
Age	7.19 (1.23)	0.2*	0.04 (0.01)	0.21	0.015*	0.04 (0.02)	0.21*	0.04 (0.02)	0.25	0.024*	0.0 (0.02)	0.02	−0.01 (0.02)	−0.05	0.707
Sex (males vs. females)[d]	−0.24 (0.34)	−0.05	−0.1 (0.34)	−0.02	0.772	−0.04 (0.38)	−0.01	−0.02 (0.38)	0.0	0.961	−0.42 (0.47)	−0.09	−0.2 (0.46)	−0.04	0.665
Comorbid conditions (total number)	−0.12 (0.11)	−0.09	−0.11 (0.11)	−0.08	0.329	−0.27 (0.14)	−0.18	−0.3 (0.14)	−0.2	0.03*	−0.08 (0.18)	−0.05	−0.04 (0.17)	−0.03	0.799
Prior cancer history (no vs. yes)[d]	−1.18 (0.85)	−0.22	−1.02 (0.83)	−0.19	0.221	–	–	–	–	–	–	–	–	–	–
Disease stage (early vs. late)[d]	−0.78 (0.38)	−0.17*	−0.7 (0.37)	−0.15	0.043*	0.04 (0.47)	0.01	−0.01 (0.47)	0.0	0.979	−0.87 (0.61)	−0.17	−0.7 (0.59)	−0.13	0.242
Time from diagnosis	0.0 (0.0)	−0.1	0.0 (0.0)	−0.09	0.204	–	–	–	–	–	–	–	–	–	–
Previous chemotherapy experience (yes vs. no)[d]	−1.39 (0.93)	−0.24	−1.39 (0.9)	−0.24	0.127	1.13 (0.51)	−0.08*	1.22 (0.51)	0.2	0.019*	0.64 (0.61)	0.11	0.59 (0.59)	0.1	0.32
Surgery prior to adjuvant chemotherapy ± radiotherapy (no vs. yes)[d]	−0.03 (0.07)	−0.03	0.05 (0.08)	0.06	0.507	−0.08 (0.12)	−0.08	−0.1 (0.13)	−0.11	0.423	0.03 (0.11)	0.03	0.08 (0.11)	0.09	0.457
Treatment modalities received (single vs. combined)[d]	–	–	–	–	–	0.6 (0.6)	0.12	0.59 (0.61)	0.12	0.335	−0.15	0.92	−0.42 (0.88)	−0.05	0.638
Chemotherapy emetogenicity	–	–	–	–	–	0.15 (0.46)	0.03	0.13 (0.45)	0.03	0.778	−0.67 (0.54)	−0.14	−0.72 (0.51)	−0.15	0.164
Antiemetics received (no vs. yes)[d]	–	–	–	–	–	−0.29 (0.68)	−0.04	−0.56 (0.68)	−0.08	0.41	−0.29 (1.01)	−0.03	0.13 (0.98)	0.01	0.893
Treatment duration	–	–	–	–	–	0.0 (0.0)	0.08	0.0 (0.0)	0.08	0.41	0.0 (0.0)	−0.11	0.0 (0.0)	−0.08	0.408
Overall QoL (pretreatment)	–	–	–	–	–	0.44 (0.09)	0.42***	0.42 (0.09)	0.41	<0.001***	0.01 (0.12)	0.01	0.04 (0.11)	0.04	0.725
Overall QoL (on-treatment)[d]	–	–	–	–	–	–	–	–	–	–	0.52 (0.12)	0.52***	0.52 (0.11)	0.53	<0.001***
Nausea incidence (no vs. yes)[d]	–	–	–	–	–	–	–	–	–	–	–	–	−1.24 (0.45)	−0.27	0.008**
Vomiting incidence (no vs. yes)[d]	–	–	–	–	–	–	–	−1.26 (0.54)	−0.21	0.021*	–	–	–	–	–
Appetite loss incidence (no vs. yes)[d]	–	–	−1.54 (0.52)	−0.23	0.003**	–	–	–	–	–	–	–	–	–	–

GI gastrointestinal, *QoL* quality of life, *B* unstandardised regression coefficient, *SE* standard error of B, *β* standardised regression coefficient

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

[a] $R^2 = 0.07$ for step 1, $\Delta R^2 = 0.05$ for step 2 ($p = 0.003$)

[b] $R^2 = 0.28$ for step 1, $\Delta R^2 = 0.05$ for Step 2 ($p = 0.012$)

[c] $R^2 = 0.42$ for step 1, $\Delta R^2 = 0.06$ for step 2 ($p = 0.008$)

[d] Dichotomised variables; the first category in parentheses is the reference group

Table 5 The contribution of nausea, vomiting and appetite loss as part of a GI symptom cluster to overall QoL impairment across treatment after adjusting for demographics, clinical variables and overall QoL at pretreatment (baseline) in a linear mixed model analysis (N=200)

Independent variable/predictor/parameter	Parameter estimate (b)	Standard error (SE)	95 % confidence interval (CI)	p
Intercept/constant	1.15	0.59	−0.11, 2.32	0.052
Age	0.02	0.01	0.0, 0.03	0.028*
Sex (male vs. female)[a]	−0.16	0.17	−0.49, 0.18	0.356
Comorbid conditions (total number)	0.11	0.06	0.01, 0.22	0.068
Disease stage (early vs. late)[a]	−0.29	0.21	−0.69, 0.12	0.161
Previous chemotherapy experience (yes vs. no)[a]	0.51	0.22	0.08, 0.93	0.019*
Surgery prior to adjuvant chemotherapy ± radiotherapy (no vs. yes)[a]	−0.05	0.2	−0.44, 0.34	0.79
Treatment modalities received (single vs. combined)[a]	−0.17	0.25	−0.67, 0.32	0.493
Treatment duration	0.0	0.0	0.0, 0.0	0.268
Overall QoL (pretreatment)	0.69	0.04	0.62, 0.77	<0.001***
Nausea incidence (no vs. yes)[a]	−3.67	1.16	−5.95, −1.38	0.002
Vomiting incidence (no vs. yes)[a]	−0.08	0.25	−0.57, 0.42	0.757
Appetite loss incidence (no vs. yes)[a]	−0.1	0.32	−0.73, 0.52	0.753
Nausea × vomiting incidence (no vs. yes)[a]	−3.62	1.21	−6.0, 1.25	0.003**
Nausea × appetite loss incidence (no vs. yes)[a]	−4.04	1.39	−6.79, −1.3	0.004**
Vomiting × appetite loss incidence (no vs. yes)[a]	−0.32	0.4	−1.11, 0.48	0.431
Nausea × vomiting × appetite loss incidence (no vs. yes)[a]	−4.53	1.46	−7.39, −1.67	0.002**

GI gastrointestinal, *QoL* quality of life

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

[a]Dichotomised variables; the first category in parentheses is the reference group

Discussion

This study demonstrated that cancer patients experience multiple concurrent symptoms during treatment that interact to exert synergistic effects on patient outcomes such as QoL, in a manner that is different from that of individual symptoms alone. From a clinical perspective, recognition of a consistent symptom cluster involving nausea, vomiting and appetite loss is important given the great difficulties clinicians have experienced in treating nausea per se, and may suggest therapeutic strategies not previously considered.

Statistical validity and reliability of a GI symptom cluster containing nausea, vomiting and appetite loss

Patients with mixed diagnoses exhibited a GI cluster consisting exclusively of nausea, vomiting and appetite loss before, during and at the end of combined modality treatment. Unsurprisingly, patients who experience TIN+/−V tend to develop appetite loss due to the negative association between food intake and TIN+/−V [36, 37], and patients in the present study were no exception.

GI symptom clusters have commonly been identified in studies of both homogeneous and heterogeneous cancer patients, often including N&V alone (e.g. [38–40]) or with appetite loss, taste alteration, diarrhoea and/or bloating (e.g. [21, 40–42]). Nevertheless, only a few studies have found a GI symptom cluster comprising solely of nausea, vomiting and appetite loss as revealed in this study [38, 40–42], and none have demonstrated symptom stability over time. Outcomes of this study suggest, perhaps convincingly for the first time, that a stable GI symptom cluster may exist independently of cancer diagnosis, disease stage, treatment type/stage and other demographic/clinical factors (e.g. age, gender, preexisting comorbidities), as has been reported elsewhere for other symptom clusters (e.g. sickness behaviour cluster) [38, 39, 42]. Nausea, vomiting and appetite loss were identified in a GI cluster with remarkable consistency across the treatment trajectory (pre-, on- and post-treatment), accounting for approximately one tenth of the explained variance in QoL and demonstrating acceptable internal consistency (Cronbach's alpha range: 0.73–0.74) at each time point. A comparable study involving 143 mixed cancer patients identified a relatively stable GI cluster over 12 months following diagnosis, but symptoms in the cluster exhibited some variability across time (N&V plus one to two other transient symptoms) and unsatisfactory internal consistency (Cronbach's alpha<0.7) on the majority of assessments [21]. The variability in GI cluster symptoms observed relative to the present study may have been due to several methodological differences (e.g. eligibility criteria, measures used, timing of assessments, chemotherapy emetogenicity, treatment duration, antiemetics prescribed, criteria used for statistical analyses) [21, 31].

Clinical validity of a GI symptom cluster containing nausea, vomiting and appetite loss

Statistically determined clusters may identify symptom clusters that are overlooked in clinical assessment, but are of little use to clinicians (and patients) unless they are shown to be clinically relevant. Few studies revealing statistically determined symptom clusters in cancer patients have attempted to demonstrate clinical significance also [43]. Clinical significance in this study was established by substantiating the hypothesis that previous chemotherapy experience would be coupled with higher scores on GI cluster symptoms (nausea, vomiting and/or appetite loss) across treatment. Similar results were also found in a cross-sectional study [39], where support was found for the hypothesis that advanced cancer patients receiving chemotherapy would have higher scores on GI cluster symptoms (nausea, vomiting) than those who were not. These findings suggest that higher GI symptom cluster distress may negatively impact on QoL and other patient outcomes [44].

Implications of a GI cluster (nausea, vomiting, appetite loss) and its individual symptoms for patients' quality of life and psychological adjustment

Clinical relevance is best demonstrated though when the presence of a symptom cluster has an impact on patient outcomes, such as QoL, psychological adjustment or survival [43, 44]. Study results suggest that the GI cluster (nausea, vomiting and/or appetite loss) had a negative impact on QoL, and more so than nausea, vomiting and appetite loss individually or nausea and/or vomiting. As expected, patients who reported the co-occurrence of nausea, vomiting and appetite loss generally experienced greater QoL impairment. Patients with these symptoms experienced worse overall QoL, overall physical health and physical, role and social functioning across treatment than those unaffected, after adjusting for differences in clinical characteristics and baseline QoL/psychological functioning between patients in univariate analyses. Greater fatigue and cancer distress were also experienced across treatment by these patients, as well as higher levels of premorbid neuroticism.

Similar outcomes have been observed previously, albeit in less expansive studies examining the impact of acute and/or delayed CINV per se on QoL [10, 13, 36]. In the most comparable study, Osoba and colleagues [36] found in an antiemetic trial of 832 mixed cancer patients that patients with delayed CINV experienced significantly worse overall QoL, physical, cognitive and social functioning, fatigue, appetite loss and sleep disturbance after one cycle of M/HEC compared to those unaffected. Additionally, in an observational study of 151 mixed cancer patients, Cohen and colleagues [10] also found that CINV had cumulative effects on QoL and suggested that the experience of CINV in earlier cycles of chemotherapy affected QoL in subsequent chemotherapy cycles.

In the current study, approximately one tenth to over one third of the explained variance in overall QoL was accounted for by the GI cluster symptoms of nausea, vomiting or appetite loss at any of the assessed time points across treatment, after adjustment for demographics, clinical characteristics and pre-/on-treatment QoL in multivariate analyses. Of the GI symptoms, appetite loss was unsurprisingly the best independent predictor of QoL impairment at pre-treatment in the *absence of chemotherapy and radiotherapy* (cf. N&V versus other GI symptoms *during treatment* as predictors of patient outcomes including symptom distress, which negatively affects QoL) [12, 21, 35, 44]. With the introduction of combined treatment, however, vomiting took precedence in the early stages (on-treatment), but by the end of treatment (post-treatment) nausea had assumed greatest importance in explaining the change in QoL for cancer patients across treatment. Consistent with previous studies, these results suggest that nausea (particularly delayed nausea over successive cycles of chemotherapy) is a more pervasive problem than vomiting or appetite loss across treatment, irrespective of antiemetic therapy, and has a significant impact on patients' QoL [1, 6, 8, 10, 18, 23, 45]. Results also suggest that, although related, nausea, vomiting and appetite loss do not appear to share a common underlying mechanism, which would explain the minimal impact of antiemetics on nausea and, to a lesser extent, appetite loss for patients in this study. Large multicentre studies are needed to further confirm these results, however, and to determine the interactive/causal nature of the relationships among these symptoms in influencing patients' QoL.

It was notable that nausea had the greatest impact of all the GI cluster symptoms on the QoL and psychological adjustment of cancer patients across treatment. Patients with nausea experienced worse overall QoL, overall physical health and physical, role and social functioning across treatment than those unaffected after adjusting for other variables. Greater fatigue, appetite loss and sleep disturbance were also experienced across treatment by these patients, as well as higher levels of premorbid neuroticism. Nevertheless, nausea was not merely additive in its impact on QoL but occurred with vomiting and appetite loss as a cluster of GI symptoms to exert a synergistic effect of multiplicative proportions on QoL. Indeed, results of the LMM analysis demonstrated that the GI symptom cluster of nausea, vomiting and appetite loss had a stronger negative impact on overall QoL across treatment than individual symptoms alone or any symptom pair within the cluster. To our knowledge, no *longitudinal* study has examined the synergistic effects of a GI cluster comprising N&V in this manner,

although the results of two smaller studies employing *cross-sectional* analyses have been broadly consistent [21, 37]. Nonetheless, further research is needed to confirm these exploratory results.

Limitations

Some limitations of this study must be acknowledged. Heterogeneity of the sample in terms of demographics and clinical characteristics may limit the generalisability of results. However, all analyses (except EFA) controlled for many potential confounding variables. Moreover, it is important to identify symptom clusters that are applicable to a variety of cancer patients, rather than being disease- or treatment-specific, as this reflects routine clinical practice. Finally, symptom assessment was limited to individual items from the EORTC QLQ-C30, which is designed to measure QoL. Ideally, more comprehensive measures (e.g. patient diaries for GI symptoms, EORTC QLQ-C30 + cancer-specific modules) would have been utilised and may have resulted in the identification of a different GI symptom cluster [37, 39]. Multicentre studies employing larger samples (involving both homogeneous and heterogeneous patients), prospective longitudinal and cross-sectional designs and more rigorous measures are therefore required.

Clinical implications

Regardless of aetiology, uncontrolled N&V often results in significant appetite and weight loss during chemotherapy, leading to prolonged recovery between cycles and increased risk for anticipatory N&V and malnutrition [45–48]. Malnutrition and weight loss, in turn, are associated with poorer prognosis, treatment tolerance and response, performance status, QoL and survival [45–48]. Combined with the findings of the present study, we recommend a symptom cluster or multiple symptom intervention approach involving a *central focus on nausea and vomiting as core symptoms*, but featuring the adaptability of a modular approach in which supplementary strategies may be appended as needed to target associated cluster symptoms (e.g. appetite/weight loss, GI reflux). In particular, clinicians should genuinely consider *combining* essential antiemetic therapies with other evidence-based pharmacological (e.g. delayed/acute nausea: psychotropics, such as olanzapine, lorazepam and mirtazapine; dopamine antagonists) [49–51] and non-pharmacological approaches (e.g. N&V: relaxation techniques, music, hypnotherapy, acupressure) [52–55]. This multifaceted intervention would not only improve prevention and control of N&V for their patients, but also reduce the synergistic effects of cluster symptoms (e.g. N&V, appetite loss) as a whole and improve QoL outcomes. Where nausea and/or vomiting and, by extension, their associated symptoms are not adequately controlled by these antiemetic-based interventions, clinicians must then contemplate supplementing evidence-based strategies that *specifically target the associated symptoms* (for instance, appetite/weight loss: pharmacological approaches—e.g. progestins ± olanzapine, corticosteroids; non-pharmacological approaches—e.g. nutritional counselling) [56–58].

Control using this approach may be sub-optimal, however, unless greater recognition, communication/understanding and assessment of nausea, vomiting and associated symptoms, including their effects, are undertaken by both clinicians and patients [8, 18]. Patients (and their caregivers) require support and education about TIN+/−V and associated symptoms (present or not) [19], particularly regarding the insidious manifestation and effects of nausea per se and delayed symptoms that occur outside treatment settings. Patients also need instruction on common-sense self-management strategies (e.g. nausea: basic dietary habits, such as avoiding fried/fatty foods) to consolidate the support and education provided [48, 59].

Acknowledgments The authors are grateful to the Cancer Council Western Australia and Murdoch University for their financial support. We would like to thank Mr Steve Pratt (Nutrition & Physical Activity Manager, Cancer Council WA) and an anonymous reviewer for their valuable comments on earlier drafts of this paper. Finally, we thank the oncology patients and staff at Royal Perth Hospital who made this research possible.

Conflict of interest None declared. The authors have no financial relationship with the organisations that provided funding for this research. Additionally, the authors have full control of all primary data and give consent to the journal to review this data if requested.

References

1. Ballatori E, Roila F, Ruggeri B, Betti M, Sarti S, Soru G, Cruciani G, Di Maio M, Andrea B, Deuson RR (2007) The impact of chemotherapy-induced nausea and vomiting on health-related quality of life. Support Care Cancer 15:179–185
2. The Italian Group for Antiemetic Research in Radiotherapy (IGARR) (1999) Radiation-induced emesis: a prospective observational multicenter Italian trial. Int Radiat Oncol Biol Phys 44:619–625
3. Booth CM, Clemons M, Dranitsaris G, Joy A, Young S, Callaghan W, Trudeau M, Petrella T (2007) Chemotherapy-induced nausea and vomiting in breast cancer patients: a prospective observational study. J Support Oncol 5:374–380
4. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L (1997) Determinants of postchemotherapy nausea and vomiting in patients with cancer. J Clin Oncol 15(1):116–123
5. Molassiotis A, Yam BMC, Yung H, Chan FYC, Mok TSK (2002) Pretreatment factors predicting the development of postchemotherapy nausea and vomiting in Chinese breast cancer patients. Support Care Cancer 10:139–145
6. Djärv T, Lagergren J, Blazeby JM, Lagergren P (2008) Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg 95(9):1121–1126

7. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Rittenberg C, Saito M, Tonato M, Warr D, ESMO/MASCC Guidelines Working Group (2010) Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 21(Suppl 5):v232–v243
8. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J (2006) Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 24(27):4472–4478
9. Ballatori E, Roila F, Ruggeri B, Porrozzi S, Iannopollo M, Soru G, Cruciani G, Daniele B, Locatelli MC, Pellissier J, Deuson R (2007) The cost of chemotherapy-induced nausea and vomiting in Italy. Support Care Cancer 15(1):31–38
10. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H (2007) Chemotherapy-induced nausea and vomiting—incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 15(5):497–503
11. Tina Shih Y, Xu Y, Elting LS (2007) Costs of uncontrolled chemotherapy-induced nausea and vomiting among working-age cancer patients receiving highly or moderately emetogenic chemotherapy. Cancer 110(3):678–685
12. Ballatori E, Roila F (2003) Impact of nausea and vomiting on quality of life in cancer patients during chemotherapy. Health Qual Life Outcomes 1:46
13. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J (2011) Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a U.S. population. Support Care Cancer 19(6):843–851
14. Martin CG, Rubenstein EB, Elting LS, Kim YJ, Osoba D (2003) Measuring chemotherapy-induced nausea and emesis. Cancer 98 (3):645–655
15. Saxby C, Ackroyd R, Callin S, Mayland C, Kite S (2007) How should we measure emesis in palliative care? Palliat Med 21 (5):369–383
16. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, Chesney M, Clark-Snow RA, Flaherty AM, Freundlich B, Morrow G, Rao KV, Schwartz RN, Lyman GH, American Society of Clinical Oncology (2011) Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 29(31):4189–4198
17. Ettinger DS, Bierman PJ, Bradbury B, Comish CC, Ellis G, Ignoffo RJ, Kirkegaard S, Kloth DD, Kris MG, Lim D, Markiewicz MA, McNulty R, Nabati L, Todaro B, Urba S, Yowell S, National comprehensive Cancer Network (NCCN) (2007) Antiemesis. J Natl Compr Canc Netw 5(1):12–33
18. Molassiotis A, Saunders MP, Valle J, Wilson G, Lorigan P, Wardley A, Levine E, Cowan R, Loncaster J, Rittenberg C (2008) A prospective observational study of chemotherapy-related nausea and vomiting in routine practice in a UK cancer centre. Support Care Cancer 16:201–208
19. Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, Daniele B, De Pouvourville G, Rubenstein EB, Daugaard G (2004) Incidence of chemotherapy-induced nausea and emesis after modern antiemetics: perception versus reality. Cancer 100:2261–2268
20. Kim HJ, McGuire DB, Tulman L, Barsevick AM (2005) Symptom clusters: concept analysis and clinical implications for cancer nursing. Cancer Nurs 28(4):270–282
21. Molassiotis A, Wengström Y, Kearney N (2010) Symptom cluster patterns during the first year after diagnosis with cancer. J Pain Symptom Manag 39(5):847–858
22. Wilson J, Plourde JY, Marshall D, Yoshida S, Chow W, Harsanyi Z, Pearen S, Darke A (2002) Long-term safety and clinical effectiveness of controlled-release metoclopramide in cancer-associated dyspepsia syndrome: a multicentre evaluation. J Palliat Care 18 (2):84–91
23. Pirri C, Katris P, Trotter J, Bayliss E, Bennett R, Drummond P (2011) Risk factors at pretreatment predicting treatment-induced nausea and vomiting in Australian cancer patients: a prospective, longitudinal, observational study. Support Care Cancer 19 (10):1549–1563
24. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
25. Ringdal GL, Ringdal K (1993) Testing the EORTC Quality of Life Questionnaire on cancer patients with heterogenous diagnoses. Qual Life Res 2:129–140
26. Selby PJ, Chapman JAW, Etazadi-Amoli J, Boyd NF (1984) The development of a method for assessing quality of life of cancer patients. Br J Cancer 50:13–22
27. Beck AT, Beck RW (1972) Screening depressed patients in family practice: a rapid technic. Postgrad Med 52:81–85
28. Horowitz M, Wilner N, Alvarez W (1979) Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209–218
29. Eysenck HJ, Eysenck SBG (1991) Manual of the Eysenck Personality Questionnaire (revised). Hodder & Stoughton, London
30. Tabachnick BG, Fidell LS (2007) Using multivariate statistics (fifth edition). Allyn & Bacon, Boston
31. Kirkova J, Walsh D (2007) Cancer symptom clusters—a dynamic construct. Support Care Cancer 15(9):1011–1013
32. Field A (2009) Discovering statistics using SPSS (third edition). Sage, London
33. Threlfall TJ, Thompson JR (2000) Cancer incidence and mortality in western Australia, 1998: a report of the western Australian cancer registry. Health Department of Western Australia, Perth
34. Cheng KK, Lee DT (2011) Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. Crit Rev Oncol Hematol 78 (2):127–137
35. Gift AG, Jablonski A, Stommel M, Given CW (2004) Symptom clusters in elderly patients with lung cancer. Oncol Nurs Forum 31 (2):203–210
36. Osoba D, Zee B, Warr D, Latreille J, Kaizer L, Pater J (1997) Effect of postchemotherapy nausea and vomiting on health-related quality of life. The Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. Support Care Cancer 5(4):307–313
37. Chen ML, Lin CC (2007) Cancer symptom clusters: a validation study. J Pain Symptom Manag 34:590–599
38. Wang SY, Tsai CM, Chen BC, Lin CH, Lin CC (2008) Symptom clusters and relationships to symptom interference with daily life in Taiwanese lung cancer patients. J Pain Symptom Manag 35: 258–266
39. Molassiotis A, Farrell C, Bourne K, Brearley SG, Pilling M (2012) An exploratory study to clarify the cluster of symptoms predictive of nausea using random forest modelling. J Pain Symptom Manag. doi:10.1016/j.jpainsymman.2011.11.003
40. Okuyama T, Wang XS, Akechi T, Mendoza TR, Hosaka T, Cleeland CS, Uchitomi Y (2003) Japanese version of the MD Anderson Symptom Inventory: a validation study. J Pain Symptom Manag 26:1093–1104
41. Evangelista AL, Santos EM (2012) Cluster of symptoms in women with breast cancer treated with curative intent. Support Care Cancer 20(7):1499–1550

42. Kim HJ, Barsevick AM, Tulman L, McDermott PA (2008) Treatment-related symptom clusters in breast cancer: a secondary analysis. J Pain Symptom Manag 36:468–479
43. Miaskowski C, Aouizerat BE, Dodd M, Cooper B (2007) Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. J Natl Cancer Inst Monogr 37:39–46
44. Aktas A, Walsh D, Rybicki L (2010) Symptom clusters: myth or reality? Palliat Med 24(4):373–385
45. Foubert J, Vaessen G (2005) Nausea: the neglected symptom? Eur J Oncol Nurs 9:21–32
46. Bergkvist K, Wengström Y (2006) Symptom experiences during chemotherapy treatment–with focus on nausea and vomiting. Eur J Oncol Nurs 10(1):21–29
47. Molassiotis A, Stricker CT, Eaby B, Velders L, Coventry PA (2008) Understanding the concept of chemotherapy-related nausea: the patient experience. Eur J Cancer Care 17:444–453
48. Nitenberg G, Raynard B (2000) Nutritional support of the cancer patient: issues and dilemmas. Crit Rev Oncol Hematol 34(3):137–168
49. Navari RM, Gray SE, Kerr AC (2011) Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 9(5):188–195
50. Licup N (2010) Olanzapine for nausea and vomiting. Am J Hosp Palliat Care 27(6):432–434
51. Perwitasari DA, Gelderblom H, Atthobari J, Mustofa M, Dwiprahasto I, Nortier JW, Guchelaar HJ (2011) Anti-emetic drugs in oncology: pharmacology and individualization by pharmacogenetics. Int J Clin Pharm 33(1):33–43
52. Lotfi-Jam K, Carey M, Jefford M, Schofield P, Charleson C, Aranda S (2008) Nonpharmacologic strategies for managing common chemotherapy adverse effects: a systematic review. J Clin Oncol 26(34):5618–5629
53. Dileo C (2006) Effects of music and music therapy on medical patients: a meta-analysis of the research and implications for the future. J Soc Integr Oncol 4(2):67–70
54. Richardson J, Smith JE, McCall G, Richardson A, Pilkington K, Kirsch I (2007) Hypnosis for nausea and vomiting in cancer chemotherapy: a systematic review of the research evidence. Eur J Cancer Care (Engl) 16(5):402–412
55. Ezzo JM, Richardson MA, Vickers A, Allen C, Dibble SL, Issell BF, Lao L, Pearl M, Ramirez G, Roscoe JA, Shen J, Shivnan JC, Streitberger K, Treish I, Zhang G (2006) Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting (review). Cochrane Database Syst Rev 2:CD002285
56. Adams LA, Shepard N, Caruso RA, Norling MJ, Belansky H, Cunningham RS (2009) Putting evidence into practice: evidence-based interventions to prevent and manage anorexia. Clin J Oncol Nurs 13(1):95–102
57. Berenstein EG, Ortiz Z (2005) Megestrol acetate for the treatment of anorexia-cachexia syndrome. Cochrane Database Syst Rev 2: CD004310
58. Navari RM, Brenner MC (2010) Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Support Care Cancer 18(8):951–956
59. Molassiotis A, Borjeson S (2006) Nausea and vomiting. In: Kearney N, Richardson A (eds) Nursing patients with cancer: Principles and practice. Elsevier, Oxford, pp 415–438