#### **ORIGINAL ARTICLE**



# A novel prospective descriptive analysis of nausea and vomiting among patients receiving gastrointestinal radiation therapy

Michael Poon  $^1$  · Jonathan Hwang  $^1$  · Kristopher Dennis  $^{2,3}$  · Carlo DeAngelis  $^1$  · Liying Zhang  $^1$  · Hans Chung  $^1$  · Jordan Stinson  $^1$  · Shun Wong  $^1$  · Natalie Pulenzas  $^1$  · Edward Chow  $^{1,4}$ 

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#### Abstract

*Purpose* Nausea and vomiting are common side effects from radiotherapy that can interfere with gastrointestinal (GI) cancer patients' quality of life (QOL). This study described the subjective experience of patients with radiation-induced nausea and vomiting (RINV) and its relation to QOL.

Methods Forty-eight patients treated with abdominal radiotherapy alone or with concomitant chemoradiotherapy were followed in a prospective study. All episodes of nausea, vomiting, and antiemetic use were recorded daily for the treatment period and the week following completion of therapy. QOL was assessed weekly using the Functional Living Index—Emesis QOL Tool (FLIE) and the EORTC QLQ-C30 core questionnaire (C30).

Results In total, 351 episodes of nausea severity, duration, onset time, and 154 outcomes of vomiting onset times and contents were documented. The median nausea severity experienced per episode was 5 (on a scale from 1 to 10), and the most common durations of nausea were 30 min or less and constant nausea all day and night. The most common location of nausea was the abdomen. Longer nausea duration, great nausea severities, and the location of nausea experienced

Introduction

outcomes

side effects of radiation therapy for gastrointestinal cancers that negatively impact quality of life (QOL) [1]. RINV necessitates costly supportive care interventions and, in severe cases, leads to treatment delays that can compromise tumor control. Despite increased recognition of the importance for supportive care in cancer and clinical antiemetic guidelines highlighting RINV as an understudied area, little progress

Radiation-induced nausea and vomiting (RINV) are common

has been made towards understanding the mechanisms underlying RINV [2].

The neurotransmitter serotonin is thought to be the most

important chemical mediator of RINV [3–5]. The gastrointestinal tract houses 90 % of the body's serotonin and is an important anatomic region with regards to RINV [6]. Radiation treatments to the upper abdomen are considered moderately emetogenic according to the ASCO and MASCC antiemetic guidelines, carrying a 60–90 % risk of inducing symptoms at some point during treatment [2, 7]. The incidence and severity

⊠ Edward Chow Edward.Chow@sunnybrook.ca

- Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
- Division of Radiation Oncology, University of Ottawa, Ottawa, ON, Canada
- <sup>3</sup> Ottawa Hospital Research Institute, Ottawa, ON, Canada
- Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

had significant adverse relationships to multiple QOL items on both the FLIE and the C30. In addition, the onset timing and number of vomiting episodes were related to the majority of all FLIE and OOL scores.

Conclusion Patient's subjective experiences of RINV directly correlated to the worsening of QOL outcomes. The identification and amelioration of these RINV experiences could improve QOL.

Radiotherapy-induced nausea and vomiting · Patient-reported

**Keywords** Radiotherapy-induced emesis ·

of which are thought to result from a combination of radiotherapy-related factors and patient-related factors [8, 9].

Understanding of RINV stems from several observational studies. The largest observational studies of RINV to date were conducted by the Italian Group for Antiemetic Research in Radiotherapy (IGARR) that followed 1954 patients [8, 10]. Of the patients that received radiation therapy (RT) to the upper abdomen within those studies, 29 % reported vomiting and 56 % reported nausea. Other smaller observational series that followed similar patients receiving abdominal or pelvic RT reported rates of nausea ranging from 63–83 % [11, 12]. However, in these trials, patients' experiences such as the severity and duration of individual RINV episodes were not reported.

While the gross incidence rates of nausea and vomiting during gastrointestinal radiation therapy have been captured in both observational and randomized trials, and the development of these symptoms has been shown to clearly worsen QOL [12, 13], other aspects that characterize the patient experience of these symptoms still need to be addressed. As such, patient-reported outcomes (PRO) are necessary in order to fully describe the extent to which RINV affect individuals [14]. Specifically, the duration, severity, and timing of symptoms are important factors that undoubtedly modulate the patient experience but have not been reliably captured in work to date. We performed a post hoc exploratory analysis of the timing, duration, and severity of symptoms.

#### Methods

## Study design

A prospective study was conducted at Sunnybrook Odette Cancer Centre. The research ethics board at the center approved the study protocol, and all patients gave written informed consent.

## Patients' inclusion and exclusion criteria

All patients aged 18 years or older who were able to provide informed consent, with a Karnofsky Performance Status (KPS) of greater than 40, a histologically, cytologically, or radiologically proven gastrointestinal (GI) tumor, and were scheduled to receive neoadjuvant long-course abdominal or pelvic radiotherapy were eligible. Patients who had received prior cranial radiotherapy, or abdominal and/or pelvic RT were ineligible. Patients who were planned to receive cranial radiotherapy or additional radiation within the 7 days following on-study abdominal or pelvic radiotherapy were also ineligible.



The specific radiotherapy, chemotherapy, and antiemetic treatment plans were left to the discretion of the treating oncologists. Radiotherapy was planned using computed tomography simulation.

#### Patient assessments

Patients were followed daily from the day of their first radiation treatment to 7 days following the completion of their scheduled treatment. For the study, nausea was defined as the feeling that one might vomit, vomiting as the bringing up of stomach contents, and retching as the attempt to bring up stomach contents without actually doing so. All episodes of nausea, vomiting, retching, and antiemetic use were recorded by patients in a diary. An individual episode was considered new only if it occurred at least 1 min following completion of the previous episode. On every treatment day, the patient met with a research assistant in person to review all episodes of RINV. They were asked to rate the severity, duration, location, and onset timing of each event. If the planned in-person meeting did not occur, attempts were made to contact the patient via telephone on the same day. QOL was assessed on a weekly basis beginning on the first day of treatment using the Functional Living Index—Emesis Quality of Life Tool (FLIE) and the EORTC QLQ-C30 (QLQ-C30) core questionnaire (Appendix 1). This provided a nausea and vomiting-specific QOL assessment (18-item FLIE) commonly employed in antiemetic research, while still capturing overall QOL across functional scales (30-item QLQ-C30). When data was incomplete, patients were prompted at the time of collection to recall the missing symptom or antiemetic data if possible. Patients were followed until the seventh day after their final treatment, or until they requested to be taken off the study.

#### **Outcomes of interest**

- Nausea severity, duration, location, and onset time and vomiting onset times.
- 2) The relationship between QOL as evaluated by the FLIE and QLQ-C30 and patient-reported outcomes.

#### Statistical analysis

Data analysis included all patients who were followed longitudinally. The symptoms of vomiting and retching were reported as a single composite event of "vomiting" as is common within the RINV and CINV literature to enable comparisons with historical data. The incidence of patient-reported outcomes was tabulated, and the frequencies were expressed



as total values and proportions of outcomes. Descriptive statistics summarized baseline and outcome data. Demographic information was summarized as mean, standard deviation (SD), median, and range for continuous variables and as proportions for categorical variables.

FLIE was collected for the past 3 days, but PRO data was collected daily. Therefore, to correlate FLIE data against the daily PRO data, we took the last 3 days of PRO records for each week to compare with the FLIE. C30 was collected for the past week, so we used full week C30 data and daily PRO data for analysis. To search for significant relationship between PRO and QOL (FLIE + C30) scores over time, general linear mixed model (GLMM) was used. The fixed effects included time (weeks) and categorical variables of PRO. Individual patient was considered as the random effect. The outcome was the time-dependent QOL values (natural log-transformation was applied as needed). *p* values less than 0.05 were considered statistically significant. Analyses were performed using the Statistical Analysis Software package (SAS version 9.3 for Windows).

#### Results

#### **Descriptive statistics**

A total of 51 patients were consented for follow-up; however, 3 patients did not receive radiation therapy. Therefore, only forty-eight patients planned to receive curative or palliative intent abdominal and/or pelvic radiotherapy alone or with concomitant chemoradiotherapy were followed longitudinally [12].

Patient demographics are listed in Table 1. All patients who received treatment were included in the analysis. Fifty-eight percent of patients received XRT alone, and 42 % received XRT and CT concurrently. Of those receiving XRT alone, 15 % received palliative and 85 % received potential curative treatment. The median number of treatment days was 22 (range 1–58). Ninety-two percent of patients radiotherapy treatments were targeted to the abdomen, and 8 % targeted the pelvis. In total, 332 episodes of nausea severity, 351 nausea durations, 322 nausea onset times, and 347 localization outcomes of nausea were documented (Table 2). In addition, 154 outcomes of vomiting onset times and 133 vomiting contents were documented for 48 patients who received radiation to the GI tract (Table 2). Out of the cumulative total of 1504 assessable days for these patients, 58 days' worth or 3.9 % of the data was missed.

The mode and median nausea severity experienced per episode was 5 (on a scale from 1 to 10). Given the variation in nausea duration data and the manner in which patients reported, post hoc categories for duration were created. The categories of "constant" and "on and off" were reported

Table 1 Patient demographics, radiotherapy (RT), chemotherapy, and antiemetic details

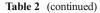
Patient characteristics	
Number of patients	48
Age (years)	
Mean $\pm$ SD	$64.7 \pm 12.8$
Median (range)	65 (32–92)
Sex	
Female	24 (50.0 %)
Male	24 (50.0 %)
Primary cancer site	
Pancreas	14 (29.2 %)
Esophagus	7 (14.6 %)
Liver	7 (14.6 %)
Colon	5 (10.4 %)
Stomach	5 (10.4 %)
Others	10 (20.8 %)
Radiation therapy (RT) characteristics	
RT Duration (days)	
$Mean \pm SD$	$26.5 \pm 16.4$
Median (range)	22 (1–58)
Anatomic site of RT	
Pancreas	14 (29.2 %)
Liver	10 (20.8 %)
Esophagus	7 (14.6 %)
Upper abdomen	6 (12.5 %)
Stomach	4 (8.3 %)
Pelvis	4 (8.3 %)
Colon	3 (6.25)
RT emetogenicity risk level	
Low	13 (27.1 %)
Moderate	35 (72.9 %)
RT technique	
IMRT	30 (62.5 %)
Field based	7 (20.19 %)
SBRT	8 (16.7 %)
Conventional 3DRT	3 (6.2 %)
Chemotherapy (CT) characteristics	
CT planned concurrently	
No	28 (58.3 %)
Yes	20 (41.7 %)
CT received	
Capecitabine	7 (35.0 %)
Infusional 5-fluorouracil	8 (45.0 %)
FU and mitomycin	2 (10.0 %)
FU and cisplatin	3 (15.0 %)
CT emetogenicity risk level	
High	3 (15.0 %)
Low	17 (85.0 %)

FU fluorouracil, RT radiotherapy, FUCISP fluorouracil cisplatin, IMRT intensity modulated radiotherapy, SBRT stereotactic body radiotherapy



**Table 2** Frequencies of nausea and vomiting patient-reported outcomes, including duration, severity, location, and onset time, among all available records

Mean number of episode per patient $\pm$ SD  Median number of episodes per patient (percent)  1 2 3 4 5 66 6 7 30 8 9 10 Duration $(n = 351)$ A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location $(n = 347)$ A: abdomen B: abdomen $+$ other site C: head D: head $+$ other site C: head D: head $+$ other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food	
Mean number of episode per patient $\pm$ SD  Median number of episodes per patient (percent)  1 2 3 4 5 62 4 5 66 6 7 8 9 10 7 Duration $(n = 351)$ A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location $(n = 347)$ A: abdomen B: abdomen + other site C: head D: head + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food	
Median number of episodes per patient (percent)  1 2 3 4 5 6 6 6 7 30 8 9 10 Duration (n = 351) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location (n = 347) A: abdomen B: abdomen B: abdomen B: abdomen C: head D: head + other site C: head D: head + other site G: not specified/not localized Onset time (n = 322) AM PM All day/night Not specified Vomiting PRO Onset time (n = 154) AM PM All day Not specified Contents (n = 133) A: food  3 4 7 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8	32
1 9 6 2 47 3 62 47 3 62 47 3 62 4 47 43 5 66 6 36 6 36 7 30 8 28 9 4 6 10 7 6 10 10 10 10 10 10 10 10 10 10 10 10 10	$.66 \pm 2.10$
2 3 4 4 5 6 6 6 6 7 30 8 9 10 7 Duration (n = 351) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location (n = 347) A: abdomen B: abdomen + other site C: head D: head + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time (n = 322) AM PM All day/night Not specified Vomiting PRO Onset time (n = 154) AM PM All day Not specified Contents (n = 133) A: food  3 6 6 6 7 3 6 6 6 7 3 6 7 8 7 8 7 8 8 9 8 9 8 8 9 8 8 9 8 9 8 8 9 8 9	.0 (1–10)
3 4 4 5 6 6 6 7 8 8 9 10 7 Duration (n = 351) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location (n = 347) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time (n = 322) AM PM All day/night Not specified Vomiting PRO Onset time (n = 154) AM PM All day Not specified Contents (n = 133) A: food  3 6 6 6 6 7 8 7 8 8 9 4 10 7 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	(2.71 %)
4	7 (14.16 %)
5 6 6 36 36 36 36 36 36 36 36 36 36 36 36	2 (18.67 %)
6 7 8 9 10 Duration (n = 351) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location (n = 347) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time (n = 322) AM PM All day/night Not specified Vomiting PRO Onset time (n = 154) AM PM All day Not specified Contents (n = 133) A: food  30 31 36 36 36 36 36 36 36 37 36 36 37 37 37 37 37 37 37 37 37 37 37 37 37	3 (12.95 %)
7 8 9 10 7 Duration (n = 351) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location (n = 347) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time (n = 322) AM PM All day/night Not specified Vomiting PRO Onset time (n = 154) AM PM All day Not specified Contents (n = 133) A: food  30 31 30 30 30 30 30 30 30 30 30 30 30 30 30	6 (19.88 %)
8 9 10 7 Duration (n = 351) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant (24 h) E: on and off F: not specified Location (n = 347) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time (n = 322) AM PM All day/night Not specified Vomiting PRO Onset time (n = 154) AM PM All day Not specified Contents (n = 133) A: food  28 28 30 30 30 30 30 30 30 30 30 30 30 30 30	6 (10.84 %)
9 10 76 Duration $(n = 351)$ A: 0–0.5 h B: >0.5–2 h C: >2–14 h D: constant (24 h) E: on and off F: not specified Location $(n = 347)$ A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food  4 0  7 0  7 0  7 0  7 0  7 0  7 0  7 0	0 (9.04 %)
10       7 (1)         Duration ( $n = 351$ )       10         A: 0-0.5 h       10         B: >0.5-2 h       26         C: >2-14 h       30         D: constant (24 h)       13         E: on and off       25         F: not specified       26         Location ( $n = 347$ )       26         A: abdomen       16         B: abdomen + other site       46         C: head       28         D: head + other site       21         E: neck/throat/esophagus       24         F: stomach/stomach + other site       33         G: not specified/not localized       30         Onset time ( $n = 322$ )       30         AM       88         PM       10         All day/night       12         Not specified       6         Vomiting PRO       6         Onset time ( $n = 154$ )       30         All day       38         Not specified       4         Contents ( $n = 133$ )       4         A: food       31	8 (8.43 %)
Duration ( $n = 351$ )       10         A: 0-0.5 h       10         B: >0.5-2 h       26         C: >2-14 h       30         D: constant (24 h)       13         E: on and off       25         F: not specified       26         Location ( $n = 347$ )       16         A: abdomen       16         B: abdomen + other site       28         C: head       28         D: head + other site       21         E: neck/throat/esophagus       24         F: stomach/stomach + other site       33         G: not specified/not localized       30         Onset time ( $n = 322$ )       30         AM       88         PM       10         All day/night       12         Not specified       6         Vomiting PRO       6         Onset time ( $n = 154$ )       30         AM       32         PM       80         All day       38         Not specified       40         Contents ( $n = 133$ )       4         A: food       31	(1.20 %)
A: $0$ – $0$ .5 h  B: >0.5–2 h  C: >2–14 h  D: constant (24 h)  E: on and off  F: not specified  Location ( $n$ = 347)  A: abdomen  B: abdomen + other site  C: head  D: head + other site  E: neck/throat/esophagus  F: stomach/stomach + other site  G: not specified/not localized  Onset time ( $n$ = 322)  AM  PM  All day/night  Not specified  Vomiting PRO  Onset time ( $n$ = 154)  AM  PM  All day  Not specified  Contents ( $n$ = 133)  A: food	(2.11 %)
B: $>0.5-2$ h C: $>2-14$ h D: constant (24 h) E: on and off F: not specified Location ( $n = 347$ ) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time ( $n = 322$ ) AM PM All day/night Not specified Vomiting PRO Onset time ( $n = 154$ ) AM PM All day Not specified Contents ( $n = 133$ ) A: food	
C: >2-14 h  D: constant (24 h)  E: on and off  F: not specified  Location $(n = 347)$ A: abdomen  B: abdomen + other site  C: head  D: head + other site  E: neck/throat/esophagus  F: stomach/stomach + other site  G: not specified/not localized  Onset time $(n = 322)$ AM  PM  All day/night  Not specified  Vomiting PRO  Onset time $(n = 154)$ AM  PM  All day  Not specified  Contents $(n = 133)$ A: food  A: abdomen  16  25  26  26  27  28  29  29  40  20  21  24  25  26  27  27  28  29  20  20  20  20  20  20  20  20  20	06 (30.20 %)
D: constant (24 h) E: on and off F: not specified  Location ( $n = 347$ ) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time ( $n = 322$ )  AM PM All day/night Not specified Vomiting PRO Onset time ( $n = 154$ )  AM PM All day Not specified Contents ( $n = 133$ ) A: food	6 (7.41 %)
E: on and off F: not specified  Location $(n = 347)$ A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food  25 A: abdomen A:	0 (8.55 %)
E: on and off F: not specified  Location $(n = 347)$ A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food  25 A: abdomen A:	38 (39.32 %)
Location $(n = 347)$ A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food  16  28  28  28  29  20  21  21  22  30  30  30  30  30  31	5 (7.12 %)
Location $(n = 347)$ A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food  16  28  28  28  29  24  27  30  30  30  30  30  30  30  31	6 (7.41 %)
A: abdomen  B: abdomen + other site  C: head  D: head + other site  E: neck/throat/esophagus  F: stomach/stomach + other site  G: not specified/not localized  Onset time (n = 322)  AM  PM  All day/night  Not specified  Vomiting PRO  Onset time (n = 154)  AM  PM  All day  Not specified  Contents (n = 133)  A: food	,
B: abdomen + other site  C: head  D: head + other site  E: neck/throat/esophagus  F: stomach/stomach + other site  G: not specified/not localized  Onset time $(n = 322)$ AM  PM  All day/night  Not specified  Vomiting PRO  Onset time $(n = 154)$ AM  PM  All day  Not specified  Contents $(n = 133)$ A: food  A: food	65 (47.55 %)
C: head       28         D: head + other site       21         E: neck/throat/esophagus       24         F: stomach/stomach + other site       33         G: not specified/not localized       30         Onset time (n = 322)       88         PM       10         All day/night       12         Not specified       60         Vomiting PRO       0         Onset time (n = 154)       32         AM       32         PM       80         All day       38         Not specified       46         Contents (n = 133)       31         A: food       31	6 (13.26 %)
D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site G: not specified/not localized Onset time $(n = 322)$ AM PM All day/night Not specified Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified Contents $(n = 133)$ A: food  21  22  23  30  30  30  30  30  30  30  30	8 (8.07 %)
E: neck/throat/esophagus  F: stomach/stomach + other site  G: not specified/not localized  Onset time (n = 322)  AM  PM  All day/night  Not specified  Vomiting PRO  Onset time (n = 154)  AM  PM  All day  Not specified  Contents (n = 133)  A: food  A: food  A: 24  A: 32  A: 32  A: 33  A: 40  A: 32  A: 32  A: 33  A: 34  A: 35  A: 36  A: 37  A: 37  A: 37  A: 38  A: 3	1 (6.05 %)
F: stomach/stomach + other site  G: not specified/not localized  Onset time $(n = 322)$ AM  PM  All day/night  Not specified  Vomiting PRO  Onset time $(n = 154)$ AM  PM  All day  Not specified  Contents $(n = 133)$ A: food  A: food	4 (6.92 %)
G: not specified/not localized Onset time $(n = 322)$ AM  PM  All day/night Not specified  Vomiting PRO Onset time $(n = 154)$ AM  PM  All day  Not specified  Contents $(n = 133)$ A: food	3 (9.51 %)
Onset time $(n = 322)$ AM 88  PM 10  All day/night 12  Not specified 66  Vomiting PRO  Onset time $(n = 154)$ AM 32  PM 80  All day 38  Not specified 46  Contents $(n = 133)$ A: food 31	0 (8.65 %)
AM 88 PM 10 All day/night 12 Not specified 66 Vomiting PRO Onset time $(n = 154)$ AM 32 PM 80 All day 38 Not specified 46 Contents $(n = 133)$ A: food 31	( ( ) ( ) ( )
PM 10 All day/night 12 Not specified 66 Vomiting PRO Onset time $(n = 154)$ AM 32 PM 80 All day 38 Not specified 46 Contents $(n = 133)$ A: food 31	8 (27.33 %)
All day/night Not specified  Vomiting PRO Onset time $(n = 154)$ AM PM All day Not specified  Contents $(n = 133)$ A: food  12  12  13  14  15  16  17  18  18  18  18  18  18  18  18  18	07 (33.23 %)
Not specified $660$ Vomiting PRO  Onset time $(n = 154)$ AM $32$ PM $80$ All day $38$ Not specified $40$ Contents $(n = 133)$ A: food $31$	21 (37.58 %)
Vomiting PRO Onset time $(n = 154)$ AM AM PM All day Not specified Contents $(n = 133)$ A: food  32 40 Contents ( $n = 133$ )	(1.86 %)
Onset time $(n = 154)$ AM 32  PM 80  All day 38  Not specified 40  Contents $(n = 133)$ A: food 31	(1.00 /0)
AM 32 PM 80 All day 38 Not specified 40 Contents $(n = 133)$ A: food 31	
PM 80 All day 38 Not specified 40 Contents $(n = 133)$ A: food 31	2 (20.78 %)
All day 38  Not specified 4 (  Contents $(n = 133)$ A: food 31	0 (51.95 %)
Not specified 4 Contents $(n = 133)$ A: food 31	8 (24.68 %)
Contents $(n = 133)$ A: food 31	
A: food 31	(2.60 %)
	1 (22 21 0/)
B: 1000 + otner 36	1 (23.31 %)
	6 (27.07 %)
	9 (14.29 %)
•	4 (10.53 %)
E: not specified/other 33  No. of episodes	3 (24.81 %)



Nausea PRO	
N	1442
Mean $\pm$ SD	$0.16\pm0.70$
Median (range)	0 (0–6)

AM morning, PM afternoon

directly by patients and were defined as nausea without a clear period of respite and nausea throughout the day but with intermittent asymptomatic periods, respectively. The most common durations of nausea were 2–14 h and constant nausea. With regards to onset timing, the original intent was to capture the exact times of onset of symptoms; however, after a few weeks, patients were frustrated as it was too demanding. Patients would have to be prompted during daily meetings with research assistants in person. As such, the pragmatic decision was made to change the timing into morning (defined as onset beginning in AM hours) and evening (defined as onset beginning in PM hours). The onset time of nausea was found it be equally likely in the morning, afternoon, or all day. In contrast, vomiting was more likely to begin in the afternoon and the most common content of vomiting was food.

The location of nausea was categorized primarily by primary location of nausea and by whether or not patients listed a secondary site. The most common area patients localized nausea to was solely the abdomen. This was followed by patients who reported their nausea to be localized to the abdomen plus an additional location.

#### Relationship patient-reported outcomes and 18-item FLIE

The aforementioned nausea patient-reported outcomes demonstrated significant relationships with many aspects of QOL as measured by the FLIE. Increased nausea duration has a significant adverse relationship with 5 QOL items as measured by the FLIE (Q1 (p = 0.04), Q6 (p = 0.04), Q11 (p = 0.02), Q12 (p = 0.04), and Q15 (p = 0.03) (Table 3). Patients with fewer hours of nausea duration had fewer troubles on QOL (negative coefficient for Q1 and Q12; but positive coefficient for Q6, Q11, and Q15). After adjusting for nausea duration, FLIE items/summary scores had no significant time trends, except for Q3 (increasing over time, indicating less problem). Nausea location had significant relationship with 8 FLIE items Q2, Q3, Q6, Q7, Q8, Q11, Q15, and Q16. For each above items, the most significant locations were head, head + other, abdomen + other, neck/throat/esophagus, and stomach/stomach + other (Table 3). There were significant relationship between nausea severity and FLIE item Q2, vomiting FLIE items of Q10-18, and vomiting summary score (Table 3). Patients with higher nausea severities were more likely to have more troubles on all the listed FLIE items



Table 3 Relationship between FLIE (item 1-18 and Summary scores) and nausea duration, nausea location, nausea severity, vomiting onset time, and vomiting episodes over time

Тоб	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting onset	p value	Vomiting episodes	p value
RINV QI	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.1236 0.0376* 0.0119* 0.0077* 0.00206* 0.1004	Time  Nausea location (vs. not specified)  A: abdomen  B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.3028 0.5801 0.6255 0.6867 0.3012 0.617 0.555	Time Nausea severity	0.0381* 0.2399	Time Vomiting onset (vs. all day) AM PM	0.0286* 0.0016* 0.0006* 0.0023*	Time Vomiting episodes	0.4193 <0.0001*
RINV Q2	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.3166 0.0888 0.0268 0.0259 0.0178 0.1515	Time  Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: Head + other site E: neck/throat/esophagus E: stomach/stomach + other site	0.7172 0.0129* 0.2816 0.9638 0.1724 0.0696 0.5207	Time Nausea severity	0.0102*	Time Vomiting onset (vs. all day) AM PM	0.1161 0.0020* 0.0013*	Time Vomiting episodes	<pre> 0.0898   &lt;0.0001*</pre>
RINV Q3	Time  Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.0212* 0.1726 0.036 0.3697 0.0597 0.0597 0.3429	Time  Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.0929 0.0453* 0.1387 0.8442 0.414 0.4342 0.1196	Time Nausea severity	0.2765	Time Vomiting onset (vs. all day) AM PM	0.0485* 0.0025* 0.0012* 0.0026*	Time Vomiting episodes	0.2265 <0.0001*
RINV Q4	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.1573 0.1691 0.3894 0.0398 0.0501 0.4423	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.3429 0.1656 0.0826 0.7722 0.6337 0.7871 0.7439	Time Nausea severity	0.1389	Time Vomiting onset (vs. all day) AM PM	0.0336* 0.0228* 0.0134*	Time Vomiting episodes	0.2245
RINV Q5	Time Nausea duration (vs. not specified)	0.1116	Time Nausea location (vs. not specified)	0.5702	Time Nausea severity	0.0938	Time Vomiting onset (vs. all day)	0.0592 <b>0.0068</b> *	Time Vomiting episodes	0.1593



Table 3 (continued)

ation p value Nanseu location p value Nansea severity p value vontingo onest p value of 1232 A. abdomen other site of 1243 A. abdomen volter site of 1244 A											
A. O. d. 3. h         o. 42.2. o. 1.03         A. abdomen         0.1835         A. M.         AM         0.00129           C. >2-1.4.h         0.1376         B. abdomen volher site         0.1662         A. A. B. A. B. A. B. A. B. B. abdomen volher site         0.1663         A. B.	Тод	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting onset	p value	Vomiting episodes	p value
R. A. Constant   C. A. A. A. A. Colombia   C. A. C. A.		0	000	-				, i	4000		
B. 20.5-2   D. 12.05   B. abdoment - other site   0.1772   D. 12.05     C. 2-14   D. 12.08   C. band - other site   0.245     D. constant   0.285   D. band - other site   0.245   Time   0.1506   Time   0.1280     D. constant   0.0283   D. band - other site   0.0459   Time   0.1290   Time   0.1280     D. constant   0.0424   Nates becafied   0.0459   Nates severity   0.121   Variating onst - 0.1200     D. constant   0.0474   A. abdomen - other site   0.0459   A. abdomen - other site   0.0459   Time   0.1201   A. abdomen - other site   0.0459   Time   0.2850   Time   0.0014     D. constant   0.0378   D. band - other site   0.0159   Time   0.2978   Time   0.1201   A. abdomen - other site   0.0164   A. abdomen - other site   0.0165   A. abdomen - other site   0.045   A. abdomen - other site   0.0450   A. abdomen - other site   0.0450   A. abdomen - other site   0.4951   A. Abdomen		A: 0-0.5 h	0.4232	A: abdomen	0.1835			AM	0.0018*		
Deconstant   0.885   Cabada		B: $>0.5-2 \text{ h}$	0.1205	B: abdomen + other site	0.7672			PM	0.0223*		
D. constant         0.8853         D. bradt - other site         0.6818         Time         0.1366         Time         0.1289         Time <th< td=""><td></td><td>C: &gt;2-14 h</td><td>0.2188</td><td>C: head</td><td>0.2163</td><td></td><td></td><td></td><td></td><td></td><td></td></th<>		C: >2-14 h	0.2188	C: head	0.2163						
E: on and off		D: constant	0.8853	D: head + other site	0.6342						
Time         0.0129         Time         0.129         Time         0.1284         Time         0.1284         Time         0.1284         Time         0.1284         Time         0.1284         Time         0.01244         Nance duration         0.0154         Nance duration         0.0154         Nance severily         0.12         Nation of time         0.0154         Nance severily         0.12         Nation of 0.0001         0.0001         A.0.0001		E: on and off	0.9546	E: neck/throat/esophagus	0.6818						
Time         0.4253         Time         0.5234         Time         0.1529         AM         0.1001*         0				F: stomach/stomach + other site	0.9129						
Namecal duration         0.00245         A naveal location         0.0150+         Namecal duration         0.00744         A. and specified)         0.0059-         Namecal current         (78. all day)         (78. all day)         (79. all day) <td>RINV Q6</td> <td>Time</td> <td>0.2553</td> <td>Time</td> <td>0.5248</td> <td>Time</td> <td>0.1506</td> <td>Time</td> <td>0.1289</td> <td>Time</td> <td>0.2808</td>	RINV Q6	Time	0.2553	Time	0.5248	Time	0.1506	Time	0.1289	Time	0.2808
(vs. not specified)         (vs. not specified)         (0.069)         AM         (vs. not specified)           Bs-96-2-1h         0.0642         B: abdomen + other site         0.5783         AM         40.0001*           Cr>5-14h         0.0678         C: head         0.0778         C: head         0.0783         PM            D: constant         0.0318         D: thad + other site         0.1038*         D: thad + other site         0.0138*         The net/throat/copingus         0.0128*         PM		Nausea duration	0.0424*	Nausea location	0.0150*	Nausea severity	0.121	Vomiting onset	<0.0001*	Vomiting episodes	<0.0001*
B::045-21 in constant         0.0542         3. abdomen + other site         0.2569         ANY         C0001*         CO001*         C		(vs. not specified)	***************************************	(vs. not specified)	00900			(vs. all day)	*10000/		
C: 2-14 in Constant         O.0318*         D: head + other site         0.0015*         Proposition         Proposition </td <td></td> <td>A: 0-0.3 II D: \0 £ 2 h</td> <td>0.00/4</td> <td>A: abdomen D: abdomen ± other site</td> <td>0.0099</td> <td></td> <td></td> <td>AIM</td> <td>\0.0001 \0.0001</td> <td></td> <td></td>		A: 0-0.3 II D: \0 £ 2 h	0.00/4	A: abdomen D: abdomen ± other site	0.0099			AIM	\0.0001 \0.0001		
C: >2-14 II         0.0016*         0.0015*         C: read           D: constant         0.4318*         D: head         0.0128*         C: p.		D: /0.3-2 II	7100.0	D. abdolliell + Oulel site	0.000			FINI	-0.0001		
D: constant         0,0318*         D: head+ other site         0,0015*           E: on and off         0,2389         E: newthytomach - other site         0,019*         1.00.58         Time         0,5319         Time         0,0378         Time         0,0044*           A: O-0.5 h         Time         0,643         Time         0,643         Time         0,0044*         Anisas accepting 0,1976         Anisas accepting 0,0044*		C: >2–14 h	0.0076*	C: head	0.2783						
E. on and off         0.3289         E: neek/throat/stonach + other site         0.0128*         C.0199*         Time         0.02978         Time         0.0286           Nausea durnion         0.634         Time         0.6319         Timing ones         0.0044*         Nantange durnion         0.0412*         Nausea severity         0.1976         Yoning ones         0.0044*           Aco-0.5 h         0.0949         A: abdomen + other site         0.4059*         AM         AM         0.0018*           C: >2-14 h         0.0408         C: bread + other site         0.4771         AM         0.0054*         AM         0.0054*           D: constant         0.2509         E: neck/throat/esophagus         0.8584         A         AM         0.0026*           Ava. o.0.5         Image durnion         0.1095         Nausea durnion         0.1043         Nausea severity         0.3343         Time         0.0297         PM         0.0026*           Ava. o.0.5         Image blocation         0.0483         Nausea severity         0.309         Yoning onset         0.0026*           Ava. o.0.5         Image blocation         0.1043         Nausea severity         0.1044         Am         0.0027*           Ava. o.0.5         Image blocation		D: constant	0.0318*	D: head + other site	0.0015*						
Time         0.643         Time         0.0199*         Time         0.6319         Time         0.6319         Time         0.6389         Time         0.6319         Time         0.6319         Time         0.0142*         Nauesa severity         0.1976         Voniting ones         0.0044*           At .0.5 h         At .2 abdomen + other site         0.4995         Att. abdomen + other site         0.4831         Att. abdomen + other site         0.4831         Att. abdomen + other site         0.4831         Att. abdomen + other site         0.4838         Att. abdomen + other site         0.4839         Att. abdomen + other site         0.7394         Att. abdomen + ot		E: on and off	0.3289	E: neck/throat/esophagus	0.0128*						
Time         0.643         Time         0.6319         Time         0.2978         Time         0.0366           Naasea duration         0.1803         Naasea fortion         0.0142*         Nausea severity         0.1976         Voniting onset         0.0044*           A: Do. S. Look         A: abdomen + other site         0.2194         A: abdomen + other site         0.0495         A: A.				F: stomach/stomach + other site	0.0199*						
Nausea duration         0.1803         Nausea location         0.0142*         Nausea severity         0.1976         Vomiting one         0.0044*           A: 0-0.5 h         0.02.2 h         A: abdomen         0.2194         A: abdomen         0.4995         A: A         AM         0.0018*           B: 0-0.5 h         0.02.2 h         B: abdomen + other site         0.4995         AM         AM         0.0018*           C: 2-14 h         0.0408         C: head         0.4995         AM         AM         0.0018*           D: constant         0.2519         D: head + other site         0.4995         AM         0.3029         B: abdomen + other site         0.483         Nausea soverity         0.3343         Time         0.0018*           Nausea duration         0.1695         Nausea location         0.483         Nausea soverity         0.3094         AM         0.0018*           Nausea duration         0.1697         R: abdomen + other site         0.4898         Nausea soverity         0.3040         AM         0.012*           D: constant         0.1015         B: abdomen + other site         0.4991         Am         0.012*         A           D: constant         0.1013         C: bead         Other site         0.4991	RINV Q7	Time	0.643	Time	0.5319	Time	0.2978	Time	0.0586	Time	0.0525
(vs. not specified)		Mansea duration	0.1803	Nonesa location	0.0142*	Mansea sexterify	0.1976	Vomiting onsot	0.0044*	Vomiting onicodes	*10000
A. D. D. Sh         O. 0.0221         B. abdomen + other site         0.0495         A. abdomen         O. 0.059*         PM         PM         0.0018*           C. > 2-14 h         0.0408         C. head         0.0408         C. head         0.0408*         0.0408*         0.0405* <td></td> <td>(vs. not specified)</td> <td>0.1903</td> <td>(vs. not specified)</td> <td>7+10.0</td> <td>Nausca sevenity</td> <td>0.1970</td> <td>(vs. all dav)</td> <td>1100.0</td> <td>volunting episodes</td> <td>10000</td>		(vs. not specified)	0.1903	(vs. not specified)	7+10.0	Nausca sevenity	0.1970	(vs. all dav)	1100.0	volunting episodes	10000
B:>0.5-2 h 0021 B: abdomen + other site 0.069* C:>2-14 h 0.0408 C: head D: constant 0.2519 D: head + other site 0.4771 M: A constant 0.2519 D: head + other site 0.4771 M: A constant 0.2519 D: head + other site 0.369*  E: on and off 0.3029 E: neck/throat/esophagus 0.8884 M: A constant 0.1693 M: A constant 0.1691 M: A consta		A: 0–0.5 h	0.0949	A: abdomen	0.2194			AM	0.0018*		
C: >2-14 h		B: >0.5-2 h	0.0221	B: abdomen + other site	0.4995			PM	0.0051*		
D: constant         0.2519         D: head + other site         0.4771         P. Read + other site         0.484         P. Read + other site         0.8584         P. Read + other site         0.8584         P. Read + other site         0.369         P. Read + other site         0.369         P. Read + other site         0.369         P. Read + other site         0.6515         Time         0.0483         Nausea severity         0.3009         Vomiting onset         0.027*           (vs. not specified)         (vs. not specified)         (vs. not specified)         0.0483         Nausea severity         0.3009         Vomiting onset         0.0127*           B > 0.5-2 h         0.0157         B: abdomen + other site         0.4091         AM         0.0052*           C > 2-14 h         0.021         C: head         0.4091         AM         0.011*         D. Lead + other site         0.4091         AM         0.011*           D: constant         0.1004         D: head + other site         0.7324         Time         0.7642         Time         0.7642         Time           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.7542           Vos. not specified)         c: >2.2-14 h         0.8727		C: >2-14 h	0.0408	C: head	0.0059*						
E: on and off		D: constant	0.2519	D: head + other site	0.4771						
Time         0.7775         Time         0.6515         Time         0.3343         Time         0.027*           Nausea duration         0.1695         Nausea location         0.0483         Nausea severity         0.3009         Voniting onset         0.017**           A: 0-0.5 h         0.0371         A: abdomen         0.1643         Am         Am         0.0652*           B: >0.5-2 h         0.0157         B: abdomen + other site         0.4898         Am         PM         0.0052*           C: >2-14 h         0.021         C: head         0.0091*         Am         PM         0.0121*           D: constant         0.1004         D: head+ other site         0.4941         Am         0.7642         PM         0.0121*           E: on and off         0.0834         E: neck/throat/esophagus         0.8708         Am         0.7642         Time         0.7642         Time         0.7524           Time         0.3631         Time         0.3534         Time         0.424         Nausea severity         0.1139         Voniting onset         0.759           (vs. not specified)         0.3531         Airabdomen         0.4634         Am         0.7642         Time         0.7642           B: >0.5-2-		E: on and off	0.3029	E: neck/throat/esophagus	0.8584						
Time         0.775         Time         0.645         Time         0.6483         Time         0.3343         Time         0.020%           Vs. not specified)         (vs. not specified)         (vs. not specified)         0.0483         Nausea severity         0.3009         Voniting onset         0.0177*           A: 0-0.5 h         0.0371         A: abdomen         0.1643         A. A         AM         AM         0.0052*           B: >0.5-1 h         0.0157         B: abdomen + other site         0.0091*         AM         PM         0.011*           D: constant         0.1004         D: head + other site         0.4941         A         AM         0.011*           E: on and off         0.0834         E: neck/throat/esophagus         0.8708         Time         0.7324         A           Ime         0.361         Time         0.3249         Time         0.7542         A         A           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           Vs. not specified)         As abdomen         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           C: >2-14 h         0.872 <td></td> <td></td> <td></td> <td>F: stomach/stomach + other site</td> <td>0.369</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>				F: stomach/stomach + other site	0.369						
Nausea duration (vs. not specified)         (vs. all day)	RINV Q8	Time	0.7775	Time	0.6515	Time	0.3343	Time	0.0226*	Time	0.1421
(vs. not specified)         (vs. not specified)         (vs. all day)         (vs. all day)         (vs. all day)         AM         (vs. all day)         AM         0.0052*           A: 0-0.5 h         0.0157         B: abdomen + other site         0.0491*         PM         PM         0.0121*           C: >2-14 h         0.021         C: head         0.0491*         PM         0.0121*           D: constant         0.1004         D: head + other site         0.4941         PM         0.0121*           E: on and off         0.0834         E: neck/throat/esophagus         0.8708         PM         0.7542           Time         0.3631         Time         0.7324         Time         0.7642         Time         0.7642         Time           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           (vs. not specified)         (vs. not specified)         (vs. not specified)         Am         AM         0.4827           B: >0.5-2 h         0.8727         B: abdomen + other site         0.386         PM         0.4827           C: >2-14 h         0.979         C: head         0.4634         PM         PM         0.4629 <td></td> <td>Nausea duration</td> <td>0.1695</td> <td>Nausea location</td> <td>0.0483</td> <td>Nausea severity</td> <td>0.3009</td> <td>Vomiting onset</td> <td>0.0127*</td> <td>Vomiting episodes</td> <td>&lt;0.0001*</td>		Nausea duration	0.1695	Nausea location	0.0483	Nausea severity	0.3009	Vomiting onset	0.0127*	Vomiting episodes	<0.0001*
A: 0-0.5 h         0.0371         A: abdomen + other site         0.1643         AM         0.0052*           B: >0.5-2 h         0.0157         B: abdomen + other site         0.4898         PM         0.0121*           C: >2-14 h         0.021         C: head         0.0091*         PM         0.0121*           D: constant         0.1004         D: head + other site         0.4941         PM         0.0121*           E: on and off         0.0834         E: neck/throat/esophagus         0.8708         PM         0.8456           F: stomach/stomach + other site         0.7324         Time         0.7542         Time         0.7642         Time         0.8456           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           (vs. not specified)         (vs. not specified)         (vs. not specified)         (vs. and specified)         AM         AM         0.4827           B: >0.5-2 h         0.8727         B: abdomen + other site         0.386         PM         0.5429           C: >2-14 h         0.979         C: head         0.4634         PM         PM         0.4629		(vs. not specified)		(vs. not specified)				(vs. all day)			
B: >0.5-2 h         0.0157         B: abdomen + other site         0.0091*         PM         0.0121*           C: >2-14 h         0.021         C: head         0.0091*		A: 0-0.5 h	0.0371	A: abdomen	0.1643			AM	0.0052*		
C:>2-14 h         0.021         C: head         0.0091*           D: constant         0.1004         D: head + other site         0.4941           E: on and off         0.0834         E: neck/throat/esophagus         0.8708           Time         P: stomach/stomach + other site         0.7324           Time         0.3631         Time         0.3642           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           (vs. not specified)         (vs. not specified)         (vs. abdomen + other site         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           A: 0-0.5 h         0.3531         A: abdomen + other site         0.386         AM         0.4827           B: >0.5-2 h         0.979         C: head         0.4634         PM         0.5429		B: >0.5-2 h	0.0157	B: abdomen + other site	0.4898			PM	0.0121*		
D: constant         0.1004         D: head + other site         0.4941           E: on and off         0.0834         E: neck/throat/esophagus         0.8708           Time         F: stomach/stomach + other site         0.7324         Time         0.7642         Time         0.8456           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           (vs. not specified)         (vs. not specified)         (vs. not specified)         (vs. all day)         (vs. all day)           A: 0-0.5 h         0.3531         A: abdomen + other site         0.386         AM         AM         0.5429           C: >2-14 h         0.979         C: head         0.4634         PM         0.5429         0.5429		C: >2-14 h	0.021	C: head	0.0091*						
E: on and off		D: constant	0.1004	D: head + other site	0.4941						
F: stomach/stomach + other site       0.7324       Time       0.7642       Time       0.8456         Nausea duration       0.6612       Nausea location       0.4624       Nausea severity       0.1139       Vomiting onset       0.759         (vs. not specified)       (vs. not specified)       (vs. ald day)         A: 0-0.5 h       0.3531       A: abdomen       0.4037       AM       0.4827         B: >0.5-2 h       0.8727       B: abdomen + other site       0.386       PM       0.5429         C: >2-14 h       0.979       C: head       0.4634		E: on and off	0.0834	E: neck/throat/esophagus	0.8708						
Time         0.3631         Time         0.3249         Time         0.7642         Time         0.8456           Nausea duration         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           (vs. not specified)         (vs. not specified)         (vs. all day)         (vs. all day)         (vs. all day)           A: 0-0.5 h         0.3531         A: abdomen         0.4037         AM         0.4827           B: >0.5-2 h         0.8727         B: abdomen + other site         0.386         PM         0.5429           C: >2-14 h         0.979         C: head         0.4634         R         PM         0.5429				F: stomach/stomach + other site	0.7324						
ution         0.6612         Nausea location         0.4624         Nausea severity         0.1139         Vomiting onset         0.759           pecified)         (vs. not specified)         (vs. all day)         (vs. all day)         (vs. all day)           n         0.3531         A: abdomen         0.4037         AM         0.4827           n         0.8727         B: abdomen + other site         0.386         PM         0.5429           c: head         0.4634         0.4634         0.4634	RINV Q9	Time	0.3631	Time	0.3249	Time	0.7642	Time	0.8456	Time	0.0528
pecified) (vs. not specified) (vs. all day) 0.3531 A: abdomen 0.4037 AM 0.4827 0.8727 B: abdomen + other site 0.386 PM 0.5429 0.979 C: head 0.4634		Nausea duration	0.6612	Nausea location	0.4624	Nausea severity	0.1139	Vomiting onset	0.759	Vomiting episodes	<0.0001*
0.3531 A: abdomen 0.4037 AM 0.8727 B: abdomen + other site 0.386 PM 0.979 C: head 0.4634		(vs. not specified)		(vs. not specified)				(vs. all day)			
1 0.8727 B: abdomen + other site 0.386 PM 0.979 C: head 0.4634		A: 0-0.5 h	0.3531	A: abdomen	0.4037			AM	0.4827		
0.979 C: head		B: >0.5-2 h	0.8727	B: abdomen + other site	0.386			PM	0.5429		
		C: >2-14  h	0.979	C: head	0.4634						



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Тод	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting onset	p value	Vomiting episodes	p value
	D: constant E: on and off	0.336	D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.8943 0.6272 0.3839						
RINV Q10	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.5385 0.2127 0.0465 0.0223 0.0305 0.0994 0.183	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.7734 0.1283 0.349 0.054 0.0539 0.6773 0.9768	Time Nausea severity	0.0899	Time Vomiting onset (vs. all day) AM PM	0.0848 0.0071* 0.0043*	Time Vomiting episodes	0.7749
RINV Q11	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant	0.3257 0.0201 0.0013* 0.0039* 0.0008*	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site	0.0431 0.0023 0.6761 0.0332* 0.0374*	Time Nausea severity	0.696 0.0044*	Time Vomiting onset (vs. all day) AM PM	0.7013 0.0004* 0.0007*	Time Vomiting episodes	0.0490*
RINV Q12	E: on and off Time  Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h	0.0135* 0.8756 0.0418 0.0033*	E: neck/throat/esophagus F: stomach/stomach + other site Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site	0.7483 0.6528 0.5104 0.0895 0.9147	Time Nausea severity	0.2198 0.0032*	Time Vomiting onset (vs. all day) AM	0.246	Time Vomiting episodes	0.2656
RINV Q13	C: >2-14 h  D: constant E: on and off  Time  Nausea duration (vs. not specified) A: 0-0.5 h  B: >0.5-2 h  C: >2-14 h  D: constant E: on and off	0.0027* 0.0422* 0.9485 0.1052 0.0235 0.0222 0.0059 0.0344	C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus	0.0582 0.9334 0.8114 0.5724 0.6785 0.1414 0.9103 0.0619 0.9846	Time Nausea severity	0.2048 0.0099*	PM Time Vomiting onset (vs. all day) AM PM	0.0010* 0.2149 0.0256* 0.0206*	Time Vomiting episodes	0.2399



Table 3 (continued)

Particular   Pa	Table 3 (confinded)										
The Name duration (1982) Name duration (1992) Name duration (1993) Name	Тод	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting onset	p value	Vomiting episodes	p value
Names during					0.8551						
Answer admerine         Cost specified)         0.0821         Names according south of the stand specified)         0.023         Names according specified south of the stand specified)         0.024         A manufacture of the stand specified)         0.027         A manufacture of the stand specified south of th	RINV Q14	Time	0.8659	Time	0.4003	Time	0.2824	Time	0.061	Time	0.5579
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,		Nausea duration	0.0882	Nausea location	0.0524	Nausea severity	0.0119*	Vomiting onset	0.0263*	Vomiting episodes	<0.0001*
Name of the control		(vs. not specified)	6	(vs. not specified)	0			(vs. all day)	i		
Exercise   0.005   Exercise   0.0175   Exact content of the rise   0.0175   Exercise   0.0175   Exercise   0.028   Exercise		A: 0–0.5 n	0.012	A: abdomen	0.80			AM	0.01/3*		
Continuent of the continuent of the color side of the continuent of the color side		B: >0.5-2 h	0.017	B: abdomen + other site	0.317			PM	0.0137*		
D. constant of 0.0286 D. hadd + other site 0.0758 Time 0.4795 Time		C: >2-14 h	9000	C: head	0.0277						
E. on and off   0.1076   E. neck-chroaticsophagins   0.7125   Time   0.7377   Time   0.7409   Time   0.3401		D: constant	0.0268	D: head + other site	0.9758						
F. stornach/sformach + other site   0.4554   Time   0.0454   Time   0.0544		E: on and off	0.1076	E: neck/throat/esophagus	0.7125						
Time         0.3491         Time         0.0062*         Time         0.0757         Time         0.499         Time           Ass. Lot's bridged         0.0014.5 b.         (s. not specified)         0.0024         Austean severity         0.0075*         Am         Am         0.4090*         Time           As -0.6.5 h         0.00014         Arabdomen cuber sine         0.9078         Am         Am         4.0001*         Voniting options           D: constant         0.0014*         C. head         0.0016*         D. head + other sine         0.907         Am         Am         4.0001*         Younging options           D: constant         0.0156*         D. head + other sine         0.907         Time         0.4452         Time         0.407         Time         0.4151         Younging options           Name of untime         0.568         Time         0.018*         Am         0.407         Time         0.4018         Am					0.4759						
Value of the constant o	RINV Q15	Time	0.3491	Time	0.0688	Time	0.7377	Time	0.409	Time	0.0384*
A: 0.021 A: 0.024 A: 0.02		Nausea duration	0.0344	Nausea location	0.0062*	Nausea severity	0.0094*	Vomiting onset	<0.0001*	Vomiting episodes	<0.0001*
A. 0-0.5 h		(vs. not specified)	,	(vs. not specified)				(vs. all day)			
B:-05-21h         0.0044*         C: hand         0.0060*         B. abdomen + other site         0.117         PM         0.002*           D: constant         0.0344*         C: hand         0.0660*         Amount         Amount         0.0151         Time         0.0167         Time         0.0167         Time         0.0147         Time         0.1451         Amount         0.0167         Amount         0.0168         Amount <t< td=""><td></td><td>A: 0–0.5 h</td><td>0.0021*</td><td>A: abdomen</td><td>0.9298</td><td></td><td></td><td>AM</td><td>&lt;0.0001*</td><td></td><td></td></t<>		A: 0–0.5 h	0.0021*	A: abdomen	0.9298			AM	<0.0001*		
C:>2-14h 0.0044 C: head doff of the site of 0.997 S: Parametric or of the site of 0.997 S: Parametric or of 0.156* D: head volter site of 0.997 S: Parametric or of 0.156* D: head volter site of 0.257 Time 0.4407 Time 0.1451 Time 0.458 S: Stormet/stormetry other site 0.4287 Time 0.4013* Vorniting onset 0.1451 Time 0.056 A: abdomen volter site 0.1429 A: Am dispersion 0.051 C: head 0.1429 A: Am dispersion 0.051 C: head 0.143* Vorniting onset 0.1451 Time 0.1429 A: Am dispersion 0.051 C: head 0.143* C: head 0.143* Vorniting onset 0.1401* A: boundary 0.013* C: head 0.143* C: head 0.144* C:		B: >0.5-2 h	0.0060*	B: abdomen + other site	0.117			PM	0.0002*		
D: constant         0.0156/*         D: head+ other site         0.9997         Property of the control of the c		C: >2–14 h	0.0044*	C: head	0.0060*						
E: on and off         0.0336*         E: neck/throat/esophagus         0.9612         Amount off         0.1436*         E: neck/throat/esophagus         0.9612         Time         0.4407         Time         0.1451         Time           Nausse duration         0.5618         Amase location         0.0214         Nausse severity         0.0133*         Voniting optioned         0.0015         Voniting optioned           4x.0-0.5 h         0.056         A: abdomen         0.0214         Cx.2-14 h         0.0010         B: abdomen chers site         0.1425         Am         Am         0.0011         Poniting optioned           C: 2-14 h         0.0101         B: bead chers site         0.0275         Am         0.4601         Am         0.0011         Poniting optioned           D: constant         0.015         B: bead chers site         0.2329         Mauses cherity         0.0103         Mauses location         0.752         Am         Am         0.0014         Am           Immediate on specified         0.617         Time         0.4601         Time         0.4601         Am         0.0018         Am         0.0018         Am         Am         0.0018         Am         Am         0.0018         Am         Am         0.0018         Am		D: constant	0.0156*	D: head + other site	0.9997						
Fix some advisorment + other sine   0.4825   Time   0.4407   Time   0.0417   Time   0.0417   Time   0.0257   Time   0.0251   Aviante a beard on a constant of the constant of 0.013   Sabdomen + other site   0.0252   Aviante a severity   0.0252   Aviante a s		E: on and off	0.0336*		0.9612						
Time         0.6182         Time         0.6214         Time         0.4407         Time         0.1451         Time           Nausea duration         0.0561         Arsa tea focation         0.0211         Nausea severity         0.0138         Nomiting ones         0.0155         Nomiting ones         0.0150           A: 0-0.5 h         0.010         B: abdomen + other site         0.1429         A.A         A.A         0.010         P. A           B: >0.5-14 h         0.010         B: abdomen + other site         0.1429         A.A         A.A         0.011         P. A           D: constant         0.013         D: head + other site         0.4275         A.A         A.A         0.011         P. A           D: constant         0.013         D: head + other site         0.743         A.A         0.4601         Time         0.011         P. A           D: constant         0.015         B: abdomen + other site         0.753         Time         0.4601         Time         0.4013         A.A           A: 0-0.5 h         0.012         B: abdomen + other site         0.234         Time         0.4601         Time         0.0014*         A           A: 0-0.5 h         0.012         B: abdomen + other site					0.4825						
Nausea duration         0.0561         Nause location         0.0211*         Nausea severity (s.s. not specified)         0.0214         Nausea severity (s.s. not specified)         0.0272         AM         0.0010*         Nauting episodes           D. constant         0.013         D. head+ other site         0.0272         Time         0.4601         Time         0.0018         Nausea clusted (s.s. not specified)         0.0432         Nausea severity         0.0403*         Nounting onset         0.0014*         Nausea severity         0.0103*         Nounting episodes           V. c. not specified)         0.052         A: abdomen + other site         0.2839         Time         0.0103*         Nounting onset         0.0014*         Nounting episodes           A: 0.0.3 h         0.002         A: abdomen + other site         0.2345         AM         Nounting onset         Nounting episodes           A: 0.0.2 h         O: 0.0.2 h         A: abdomen + other site         0.3346         AM         Nounting onset         Nounting episodes           C: >2-14 h         0.0102         B: abdomen + other site         0.2364 </td <td>RINV Q16</td> <td>Time</td> <td>0.6182</td> <td>Time</td> <td>0.257</td> <td>Time</td> <td>0.4407</td> <td>Time</td> <td>0.1451</td> <td>Time</td> <td>0.6193</td>	RINV Q16	Time	0.6182	Time	0.257	Time	0.4407	Time	0.1451	Time	0.6193
(vs. not specified)         (vs. not specified)         (vs. and specified)         (vs. and table)         (vs. and table) <t< td=""><td></td><td>Nausea duration</td><td>0.0561</td><td>Nausea location</td><td>0.0211*</td><td>Nausea severity</td><td>0.0133*</td><td>Vomiting onset</td><td>0.0015*</td><td>Vomiting episodes</td><td>&lt;0.0001*</td></t<>		Nausea duration	0.0561	Nausea location	0.0211*	Nausea severity	0.0133*	Vomiting onset	0.0015*	Vomiting episodes	<0.0001*
A: 0-0.5 h         0.0056         A: abdomen         0.8014*         PM         0.0011*           B: >0.5-2 h         0.0101         B: abdomen + other site         0.1429         PM         0.0011*           C: >2-14 h         0.0031         C: head         0.0275*         A         A         A         0.0011*           D: constant         0.0131         B: abdomen + other site         0.743         A </td <td></td> <td>(vs. not specified)</td> <td></td> <td>(vs. not specified)</td> <td></td> <td></td> <td></td> <td>(vs. all day)</td> <td></td> <td></td> <td></td>		(vs. not specified)		(vs. not specified)				(vs. all day)			
B: >0.5-2 h         0.0101         B: abdomen + other site         0.045s         PM         0.0011*           C: >2-14 h         0.0031         C: head         0.0252         A.243         A.243         A.243         A.243         A.243         A.243         A.243         A.2443         A.2444		A: 0–0.5 h	0.0056	A: abdomen	0.8014			AM	0.0010*		
C: >2-14 h 0.0031 C: head other site 0.0272 E: on and off 0.0051 E: neck/throat/esophagus 0.7443 Time 0.6174 Time 0.6174 Time 0.6053 Nausea duration 0.053 Nausea duration 0.055 Nausea duration 0.055 Nausea duration 0.055 Nausea location 0.0075 Nausea severity 0.0103 Nausea severity 0.0003 Nausea S		B: >0.5-2 h	0.0101	B: abdomen + other site	0.1429			PM	0.0011*		
D: constant         0.013         D: head + other site         0.9272         Resonand off         0.051         E: neck/throat/esophagus         0.7443         Resonand off         0.051         E: stomach/stomach + other site         0.6192         Resonand off         0.051         Resonand off         0.053         Time         0.4601         Time         0.3968         Time           Nausea duration         0.053         Nausea location         0.0755         Nausea severity         0.0103*         Vomiting onset         0.0042*         Vomiting opisodes           A: 0-0.5 h         0.0062         A: abdomen + other site         0.2346         R.         AM         0.0014*         Nomiting opisodes           B: >0.5-2 l 4 h         0.0102         B: abdomen + other site         0.336         R.         AM         0.0014*         Am         0.0014*         Am         O.0014*         A		C: >2–14 h	0.0031	C: head	0.0275*						
E: on and off 0.0551 E: neck/throat/esophagus 0.7443  F: stomach/stomach + other site 0.6192  Time 0.6174 Time 0.6174 Time 0.6239 Time 0.6356 Nausea severity 0.0137 (vs. not specified) 0.0062 A: abdomen and off 0.0062 A: abdomen and off 0.0056 C: head 0.0056 C: head 0.0056 C: head 0.0057 D: head + other site 0.0376 D: on and off 0.0054 E: neck/throat/esophagus 0.6801  E: on and off 0.0549 E: neck/throat/esophagus 0.6801 Time 0.5364 Time 0.5368 Time 0.5368 Time 0.5368 Vomiting episodes		D: constant	0.013	D: head + other site	0.9272						
Time         0.6174         Time         0.6183         Time         0.4601         Time         0.3968         Time           Nausea duration         0.053         Nausea location         0.0755         Nausea severity         0.0103*         Vomiting onset         0.0042*         Vomiting episodes           A: 0-0.5 h         0.0062         A: abdomen         0.2346         A. A		E: on and off	0.0551	E: neck/throat/esophagus	0.7443						
Time         0.6174         Time         0.2839         Time         0.4601         Time         0.3968         Time           Nausea duration         0.053         Nausea location         0.0755         Nausea severity         0.0103         Voniting ones         0.0042*         Voniting episodes           A: 0-0.5 h         0.0062         A: abdomen         0.2346         A. A.         AM         0.0014*         O.0074*         O.0074*           B: >0.5-14 h         0.005         C: head         0.0376         A. A.         AM         0.0073*         AM         O.0073*         AM         O.0073*         AM         O.0073*         AM         O.0074*					0.6192						
Nausea duration         0.053         Nausea location         0.0755         Nausea severity         0.0103*         Vomiting episodes         Vomiting episodes           A: 0-0.5 h         0.0062         A: abdomen         0.0346         AM         0.0014*         AM         0.0014*         PM         0.0014*           C: >2-14 h         0.0102         C: head         0.0376         A <t< td=""><td>RINV Q17</td><td>Time</td><td>0.6174</td><td>Time</td><td>0.2839</td><td>Time</td><td>0.4601</td><td>Time</td><td>0.3968</td><td>Time</td><td>0.1134</td></t<>	RINV Q17	Time	0.6174	Time	0.2839	Time	0.4601	Time	0.3968	Time	0.1134
(vs. not specified)         (vs. not specified)         (vs. all day)         (vs. all day)         (vs. all day)         AM         AM         0.0014*         AM         0.0014*         AM         0.0014*         AM         0.0014*         AM         0.0014*         AM         0.0014*         PM         0.0014*         PM         0.0014*         PM         0.0014*         PM         0.0073*         PM         0.0074*		Nausea duration	0.053	Nausea location	0.0755	Nausea severity	0.0103*	Vomiting onset	0.0042*	Vomiting episodes	<0.0001*
B:>0.5-2 h   0.0102   B: abdomen + other site   0.2346   PM   0.0073*		(vs. not specified)	0.0062	(vs. not specified)	0.8877			(vs. all day)	0 0014*		
C: >2-14 h 0.0026 C: head C: >2-14 h 0.0026 C: h 0.0026 C: head C: >2-14 h 0.0026 C: h 0		B: >0.5_2 h	0.0100	B. shdomen + other cite	0.2346			Md	0.0073*		
D: constant 0.0155 D: head + other site 0.8993 E: on and off 0.0549 E: neck/throat/esophagus 0.6801 Time 0.3269 Time 0.2364 Time 0.4514 Nausea severity 0.0078*		C. 7. 14 L	2010.0	C. Lood	25500			TATE	6,000		
D: constant 0.0155 D: head + other site 0.8993  E: on and off 0.0549 E: neck/throat/esophagus 0.6801  E: on and off 0.0549 E: neck/throat/esophagus 0.6801  F: stomach/stomach + other site 0.8149  Time 0.3269 Time 0.2364 Time 0.5486 Time 0.9166 Time 0.5718  O.5518 Vomiting episodes		C: >2-14 II	0.0020	C: nead	0.03/0						
E: on and off 0.0549 E: neck/throat/esophagus 0.6801  F: stomach/stomach + other site 0.8149  Time 0.3269 Time 0.2364 Time 0.5486 Time 0.9166 Time 0.55718  O.55718 O.6801		D: constant	0.0155	D: head + other site	0.8993						
F: stomach/stomach + other site 0.8149  Time 0.3269 Time 0.2364 Time 0.5486 Time 0.9166 Time 0.5718 0.05718 0.4514 Nausea severity 0.0078* 0.03688 Vomiting episodes		E: on and off	0.0549		0.6801						
Time 0.3269 Time 0.2364 Time 0.5486 Time 0.9166 Time 0.5718 0.65718 Nausea severity 0.0078* 0.3688 Vomiting episodes				F: stomach/stomach + other site	0.8149						
0.4514 Nausea severity 0.0078* 0.3688 Vomiting episodes	RINV Q18	Time	0.3269	Time	0.2364	Time	0.5486	Time	0.9166	Time	0.6092
			0.5718		0.4514	Nausea severity	0.0078*		0.3688	Vomiting episodes	< 0.0001 *



Table 3 (continued)

OOL	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting onset	p value	Vomiting episodes	p value
	Nausea duration (vs. not specified) A: 0–0.5 h	0.4672	Nausea location (vs. not specified) A: abdomen	0.7283			Vomiting onset (vs. all day) AM	0.1618		
	B: >0.5-2 h	0.9837	B: abdomen + other site	0.1272			PM	0.3957		
	C: >2-14 h	0.83	C: head	0.6692						
	D: constant	0.2101	D: head + other site	0.4889						
	E: on and off	0.3277	E: neck/throat/esophagus	0.7214						
			F: stomach/stomach + other site	0.9975						
RINV nausea summary score	Time	0.2021	Time	0.9151	Time	0.0695	Time	0.0454*	Time	0.1845
	Nausea duration	0.0905	Nausea location	0.0778	Nausea severity	0.3092			Vomiting episodes	<0.0001*
	(vs. not specified)		(vs. not specified)							
	A: 0–0.5 h	0.0433	A: abdomen	0.8885			Vomiting onset	0.0022*		
	B: >0.5-2 h	0.0245	B: abdomen + other site	0.9998			(vs. all day) AM	*80000		
	C: >2–14 h	0.0101	C: head	0.0747			PM	0.0029*		
	D: constant	0.116	D: head + other site	0.4694						
	E: on and off	0.3191	E: neck/throat/esophagus	0.5095						
			F: stomach/stomach + other site	0.1624						
RINV vomiting summary score	Time	0.6735	Time	0.3173	Time	0.4045	Time	0.2273	Time	0.2857
	Nausea duration	0.101	Nausea location	0.0563	Nausea severity	0.0055*	Vomiting onset	0.0013*	Vomiting episodes	<0.0001*
	(vs. not specified)	27.00	(vs. not specified)	7,000			(vs. all day)	*		
	A. 0–0.3 II	0.0145	A. abuoillell	0.7740			AIVI	/ 000.0		
	B: >0.5-2 h	0.0163	B: abdomen + other site	0.1315			PM	0.0012*		
	C: >2-14 h	0.0076	C: head	0.0472						
	D: constant	0.0366	D: head + other site	0.927						
	E: on and off	0.1048	E: neck/throat/esophagus	0.7703						
			F: stomach/stomach + other site	669.0						

Nausea location was classified as abdomen, abdomen + other sites, head, head + other sites, neck/throat/esophagus, stomach/stomach + other sites, vs. not specified. Nausea severity was used as a numeric \*p values <0.05 were considered statistically significant and are shown in bold. For multiple comparisons of nausea duration categories, comparisons were only marked with an asterisk if the overall effect of nausea duration had a p value <0.05 variable. Vomiting onset was classified as AM, PM, vs. all day. Vomiting episodes were used as a numeric variable



and vomiting summary score. Vomiting patient-reported outcomes also showed significant relationships to QOL as measured by the FLIE. There were significant relationships between vomiting onset and all FLIE items and summary scores, except for Q9 and Q18 (Table 3). There were also significant relationships between vomiting episodes and all FLIE items and summary scores, where patients with more vomiting episodes were more likely to have worse QOL (Table 3).

# Relationship patient-reported outcomes and EORTC OLQ-C30

Patient-reported outcomes demonstrated significant relationships with QOL as measured by the QLQ-C30. Nausea duration had significant relationships with C30 fatigue, pain, dyspnea, and constipation. After adjusting for nausea duration, physical, role, social functioning significantly decrease (worsen QOL) over time and emotional functioning significantly increase (improving QOL) over time. Symptom scores of fatigue, pain, dyspnea, and financial problems also increased (worsening QOL) over time; constipation and diarrhea decreased (improving QOL) over time (Table 4). Nausea location was found to have significant relationships with physical, role, and social functioning and symptoms of fatigue, appetite loss, diarrhea, and financial problems (Table 4). There were significant relationship between nausea severity and physical, role, and social functioning and symptoms of fatigue, nausea/ vomiting, appetite loss, and diarrhea (Table 4). Patients with higher nausea severities were more likely to have more troubles on the above significant functioning/symptoms scores. Finally, there were significant relationships between vomiting episodes and all scores except for role and cognitive functioning, dyspnea, and insomnia (Table 4). Patients with more vomiting episodes were more likely to have worsened QOL, except for pain, constipation, and diarrhea. However, patients with more vomiting episodes were more likely to have fewer problems with pain, constipation, and diarrhea.

#### Discussion

RINV research typically focuses on the incidence of symptoms and often neglects the subjective experience of events that debilitate patients. This prospective study characterizes these other aspects of nausea, vomiting, and retching patient-reported outcomes induced by radiotherapy for gastrointestinal cancers patients. Detailed nausea and vomiting incidence data for this patient cohort has been previously published [12] and will not be included in the study herein.

Antiemetic practice guidelines estimate 60–90 % patients who received upper abdominal radiation experience RINV [7]. This value is based on a number of studies, including a pair of landmark studies by the Italian Group of for Antiemetic

Research in Radiotherapy and was corroborated by our incidence data [8, 10, 12]. In addition, many radiation oncologists still underestimate the risk of RINV and neglect to prescribe antiemetics according to guideline recommendations [15, 16]. While this clearly highlights the importance of RINV management, proper perspective must be taken as incidence value alone does not accurately described patients' experiences with RINV.

In total, up to 351 episodes of nausea severity, duration, or onset time and up to 154 outcomes of vomiting onset times or contents were documented for 48 patients with a mean treatment length of 25.5 days. This means that, on any given day of treatment, up to 50 and 23 % of patients experience nausea and emesis, respectively. However, our data shows that the mean severity of nausea experienced was only  $4.66 \pm 2.10$ (on a scale of 1-10) and that patients experience a dichotomous pattern of duration of nausea of either 0.5 h and constant nausea. This would suggest that (1) nausea severity had a large range of values at each episode and that an individual episode may not be that severe and (2) patients could have distinct episodes of nausea which were either acute (30 min in length) or unremitting. Our data also suggests that majority (51.95 %) of vomiting episodes occur in the afternoon only. This highlights the importance of taking a 5-HT<sub>3</sub>RA in the hours prior to radiotherapy [17].

Our data indicates that worse subjective experiences of RINV showed significant correlations with essentially all aspects of QOL as measured by both the QLQ-C30 and FLIE questionnaires; the more debilitating the nausea or vomiting characteristic by a patient, the more debilitation was reflected in QOL questionnaires. While this finding is not surprising, it emphasizes that characteristics other than incidence need to be considered when creating clinical antiemetic guidelines. Currently, the fact that treatments are being directed towards a heterogeneous group of primary and metastatic tumors, in addition to different anatomic sites, is not recognized in the guidelines [17]. In addition, what is missing from most trials in literature and the guidelines is the cumulative incidence and severity of RINV [18]. We consistently undervalue the importance of the subjective experience of patients such as the pattern of nausea and vomiting, whether patients are likely to vomit daily or just once during their treatment, or whether there are periods that the symptoms are more severe. These characteristics are paramount to determining how to appropriately use antiemetics and are especially important for nausea; where there is no objective all-or-none symptom such as vomiting.

The primary challenge encountered was the feasibility of this model of data collection. It was difficult for patients to tell us exact times and to know when exactly when a symptom started and stopped. Because of this, pragmatic changes had to be made with regards to how to categorize nausea and vomiting onset timing and durations as stated previously.



Table 4 Relationship between C30 scores and nausea duration, nausea location, nausea severity, vomiting onset time, and vomiting episodes over time

OOL	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting episodes	p value
C30 physical functioning	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	<0.0001* 0.2965 0.1249 0.8592 0.6461 0.179 0.0668	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	<pre>&lt;0.0001* &lt;0.0001* 0.0487* 0.5071 0.2003 0.0047*</pre>	Time Nausea severity	<0.0019*	Time Vomiting episodes	<0.0001*
C30 role functioning	Time  Nausea duration  (vs. not specified)  A: 0-0.5 h  B: >0.5-2 h  C: >2-14 h  D: constant  E: on and off	<ul><li><b>-0.0001*</b></li><li>0.4067</li><li>0.5728</li><li>0.3602</li><li>0.8048</li><li>0.1163</li><li>0.1015</li></ul>	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.0001* 0.0004* 0.8531 0.0149* 0.0026* 0.0047*	Time Nausea severity	0.0002*	Time Vomiting episodes	<b>&lt;0.0001</b> * 0.0991
C30 emotional functioning	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.0230* 0.1391 0.5173 0.9728 0.1917 0.3814 0.242	Time  Nausea location (vs. not specified)  A: abdomen  B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.0015* 0.3604 0.0652 0.5117 0.7124 0.9602 0.6205	Time Nausea severity	0.0012*	Time Vomiting episodes	<pre>&lt;0.0001* 0.0012*</pre>
C30 cognitive functioning	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.6091 0.3882 0.9582 0.7956 0.2304 0.5126	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.7574 0.4028 0.2336 0.2361 0.3203 0.2685 0.0169	Time Nausea severity	0.7082	Time Vomiting episodes	0.0506
C30 social functioning	Time	0.0002*	Time	0.0005*	Time	0.0012*	Time	<0.0001*



<0.0001\* <0.0001\* <0.0001\* <0.0001\* <0.0001\* 0.0391\*p value \*8000.00.3215 Vomiting episodes Vomiting episodes Vomiting episodes Vomiting episodes Vomiting episodes Time Time Time Time <0.0001\* <0.0001\* 0.0081\*0.0003\*0.3209 0.9536 0.0687 p value 0.6361 Nausea severity Nausea severity Nausea severity Nausea severity Nausea severity Time Time Time Time <0.0001\* 0.0001\*0.0039\*p value 0.0202\*\*9000.0 0.0194\*0.1909 0.1589 0.9706 0.0679 0.0037 0.0832 0.0456 0.0058 0.0089 0.2748 0.8558 0.4624 0.4598 0.8655 0.5868 0.2887 0.7079 0.6626 0.3193 0.9249 0.7826 0.0291 0.8901 0.168 0.93 0.99 F: stomach/stomach + other site B: abdomen + other site E: neck/throat/esophagus E: neck/throat/esophagus E: neck/throat/esophagus E: neck/throat/esophagus B: abdomen + other site B: abdomen + other site B: abdomen + other site (vs. not specified) (vs. not specified) (vs. not specified) (vs. not specified) D: head + other site Nausea location Nausea location Nausea location Nausea location Nausea location A: abdomen A: abdomen A: abdomen A: abdomen C: head C: head Time Time Time Time <0.0001\* <0.0001\* 0.0174\*\*9600.0 p value 0.0388 0.1217 0.3505 0.0479 0.2512 0.9203 0.4925 0.1575 0.8248 0.2993 0.0777 0.8378 0.4336 0.4482 0.6994 0.5374 9696.0 0.0811 0.0861 0.2951 0.0986 0.366 0.596 0.592 (vs. not specified) (vs. not specified) (vs. not specified) (vs. not specified) Nausea duration Nausea duration Nausea duration Nausea duration Nausea duration E: on and off E: on and off E: on and off E: on and off B: >0.5-2 h B: >0.5-2 h C: >2-14 h B: >0.5-2 h B: >0.5–2 h C: >2-14 h D: constant C: >2-14 hC: >2-14 h A: 0-0.5 h D: constant D: constant A: 0-0.5 h D: constant A: 0-0.5 h A: 0-0.5 h Time Time Time Time C30 global health status C30 nausea/vomiting C30 fatigue C30 pain OOT



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Table

TOÒ	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting episodes	p value
	Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.0023* 0.0043* 0.0679 0.0697 0.5526 0.5534	Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.0581 0.5471 0.4887 0.7601 0.0654 0.2373 0.4312	Nausea severity	0.2395	Vomiting episodes	0.0003*
C30 dyspnoea	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.0238* 0.0289* 0.0533 0.0240* 0.4233 0.4537 0.5781	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.0746 0.7777 0.2844 0.7792 0.2316 0.3214 0.0595	Time Nausea severity	0.1014	Time Vomiting episodes	0.002*
C30 insomnia	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.334 0.8538 0.7391 0.9675 0.9174 0.4265	Time Nausea location (vs. not specified) A: abdomen B: abdomen + other site C: head D: head + other site E: neck/throat/esophagus F: stomach/stomach + other site	0.4471 0.4747 0.4328 0.8164 0.034 0.4447 0.6791	Time Nausea severity	0.5785	Time Vomiting episodes	0.8945
C30 appetite loss	Time Nausea duration (vs. not specified) A: 0-0.5 h B: >0.5-2 h C: >2-14 h D: constant E: on and off	0.9072 0.7789 0.7942 0.9332 0.2902 0.5408 0.9626	Time  Nausea location  (vs. not specified)  A: abdomen  B: abdomen + other site  C: head  D: head + other site  E: neck/throavesophagus  F: stomach/stomach + other site	0.9724 0.0101* 0.0723 0.037* 0.6728 0.9171 0.746	Time Nausea severity	0.9112 0.0192*	Time Vomiting episodes	<pre>&lt;0.0001*</pre>
C30 constipation	Time	0.0063*	Time	0.0014*	Time	0.0128*	Time	<0.0001*



Table 4 (continued)

(								
Тоб	Nausea duration	p value	Nausea location	p value	Nausea severity	p value	Vomiting episodes	p value
	Nausea duration (vs. not specified) A: 0-0.5 h	<b>0.0083</b> * 0.4771	Nausea location (vs. not specified) A: abdomen	0.0686	Nausea severity	0.8853	Vomiting episodes	<0.0001*
	B: >0.5-2 h	0.7451	B: abdomen + other site	0.6925				
	C: > 2-14  h	0.8297	C: head	0.0177				
	D: constant	0.9099	D: head + other site	0.5143				
	E: on and off	0.0095*	E: neck/throat/esophagus	0.0396				
			F: stomach/stomach + other site	0.3519				
C30 diarrhea	Time	0.0019*	Time	0.0005*	Time	0.0011*	Time	<0.0001*
	Nausea duration	0.5727	Nausea location	0.0131*	Nausea severity	0.0264*	Vomiting episodes	0.0369*
	(vs. not specified) A: 0–0.5 h	0.6354	(vs. not specified) A: abdomen	0.0065*				
	B: >0.5-2 h	0.6149	B: abdomen + other site	0.826				
	C: >2-14 h	0.6942	C: head	0.6756				
	D: constant	0.9285	D: head + other site	0.8848				
	E: on and off	0.2592	E: neck/throat/esophagus	0.1286				
			F: stomach/stomach + other site	0.0938				
C30 financial problems	Time	0.0202*	Time	$\boldsymbol{0.0010}^*$	Time	0.0041*	Time	0.2192
	Nausea duration	0.7986	Nausea location	0.0088*	Nausea severity	0.2568	Vomiting episodes	0.0401*
	(vs. not specified) A: 0–0.5 h	0.9055	(vs. not specified) A: abdomen	0.0070*				
	B: >0.5-2 h	0.558	B: abdomen + other site	0.0623				
	C: >2-14 h	0.7937	C: head	0.2267				
	D: constant	0.6074	D: head + other site	0.8965				
	E: on and off	0.4206	E: neck/throat/esophagus	0.1463				
			F: stomach/stomach + other site	$\boldsymbol{0.0081}^{*}$				

Nausea location was classified as abdomen, abdomen + other sites, head, head + other sites, neck/throat/esophagus, stomach/stomach + other sites, vs. not specified. Nausea severity and vomiting episodes were utilized as numeric variables

\*p values <0.05 were considered statistically significant and are shown in bold. For multiple comparisons of nausea duration categories, comparisons were only marked with an asterisk if the overall effect of nausea duration had a p value <0.05



For instance, patients who were experiencing severe nausea or vomiting were unlikely to document each episode individually. Instead, we were limited to them just reporting "constant" nausea or nausea that was "on and off". Another challenge with this model of collection was the need for daily patient encounters. We found that without the daily encounter with patients, they would neglect to fill in their diaries on a daily basis or not fill out all of the outcomes of interest (e.g., duration, onset, and severity). However, the dilemma we faced was, although patient encountered prevented missing data, it allowed patients to simplify their diary entries knowing that a research assistant would speak to them and document their symptoms anyways. Unfortunately, this simplification prevented us from acquiring the wealth of information we hoped for.

This study is also limited by its small sample size. Given the heterogeneity of the study population, further investigation is needed to confirm our findings. Patients were treated with various radiotherapy dose fractionation schedules across several different anatomic sites. In addition, different antiemetic compounds were utilized with a wide range of doses in the study herein; the inconsistency of which prevents analysis of

antiemetic efficacy. RINV symptoms past 1 week after the completion of radiation treatment were not recorded. Nonetheless, our results highlight important aspects of nausea and vomiting that plague patients receiving GI radiotherapy and suggests possible targets for future antiemetic and QOL research.

In conclusion, our study highlights important characteristics of patients' experiences of RINV of patients undergoing radiotherapy for GI malignancies and demonstrates that patients' worsening subjective experiences of RINV directly correlate to debilitation of QOL. Increased focus on the identification and amelioration of patients' subjective experiences could lead to more appropriate use of antiemetic to improve patients' QOL.

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**Conflict of interest** The authors declare that they have no competing interests.

# Appendix 1. FLIE

1. How much nausea have you had in the past 3 days?						
1	2	3	4	5	6	7
None						A great deal
2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?						
1	2	3	4	5	6	7
None						A great deal
3. Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?						
1	2	3	4	5	6	7
A great deal						Not at all
4. How much has nausea affected your ability to enjoy a meal in the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
5. How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?						
1	2	3	4	5	6	7
A great deal						Not at all
7. Has nausea affected your daily functioning in the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days.						
1	2	3	4	5	6	7
Not at all						A great deal
9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days.						
1	2	3	4	5	6	7
Not at all						A great deal



#### (continued)

1. How much nausea have you had in the past 3 days?						
10. How much vomiting have you had in the past 3 days?						
1	2	3	4	5	6	7
None						A great deal
11. Has vomiting affected your ability to maintain usual recreation or leisure activities in the past 3 days?						
1	2	3	4	5	6	7
A great deal						Not at all
12. Has vomiting affected your ability to complete your usual household tasks during the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
13. How much has vomiting affected your ability to enjoy a meal in the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
14. How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
15. How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?						
1	2	3	4	5	6	7
A great deal						Not at all
16. Has vomiting affected your daily functioning in the past 3 days?						
1	2	3	4	5	6	7
Not at all						A great deal
17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.						
1	2	3	4	5	6	7
Not at all						A great deal
18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.						
1	2	3	4	5	6	7
A great deal						Not at all

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