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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 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 QOL 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.

Keywords Radiotherapy-induced emesis · Radiotherapy-induced nausea and vomiting · Patient-reported outcomes

Introduction

Radiation-induced nausea and vomiting (RINV) are common 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 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

1 Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

2 Division of Radiation Oncology, University of Ottawa, Ottawa, ON, Canada

3 Ottawa Hospital Research Institute, Ottawa, ON, Canada

4 Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

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.

Medical treatment

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

1) 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 ± SD	64.7 ± 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 ± SD	26.5 ± 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

Nausea PRO	
Severity	
Total number of episodes	332
Mean number of episode per patient ± SD	4.66 ± 2.10
Median number of episodes per patient (percent)	5.0 (1–10)
1	9 (2.71 %)
2	47 (14.16 %)
3	62 (18.67 %)
4	43 (12.95 %)
5	66 (19.88 %)
6	36 (10.84 %)
7	30 (9.04 %)
8	28 (8.43 %)
9	4 (1.20 %)
10	7 (2.11 %)
Duration (n = 351)	
A: 0–0.5 h	106 (30.20 %)
B: >0.5–2 h	26 (7.41 %)
C: >2–14 h	30 (8.55 %)
D: constant (24 h)	138 (39.32 %)
E: on and off	25 (7.12 %)
F: not specified	26 (7.41 %)
Location (n = 347)	
A: abdomen	165 (47.55 %)
B: abdomen + other site	46 (13.26 %)
C: head	28 (8.07 %)
D: head + other site	21 (6.05 %)
E: neck/throat/esophagus	24 (6.92 %)
F: stomach/stomach + other site	33 (9.51 %)
G: not specified/not localized	30 (8.65 %)
Onset time (n = 322)	
AM	88 (27.33 %)
PM	107 (33.23 %)
All day/night	121 (37.58 %)
Not specified	6 (1.86 %)
Vomiting PRO	
Onset time (n = 154)	
AM	32 (20.78 %)
PM	80 (51.95 %)
All day	38 (24.68 %)
Not specified	4 (2.60 %)
Contents (n = 133)	
A: food	31 (23.31 %)
B: food + other	36 (27.07 %)
C: mucous/mucous + other/bile/acid	19 (14.29 %)
D: water/liquid	14 (10.53 %)
E: not specified/other	33 (24.81 %)
No. of episodes	
N	1442
Mean ± SD	0.16 ± 0.70
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

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting onset	*p* value	Vomiting episodes	*p* value
RINV Q1	Time	0.1236	Time	0.3028	**Time**	**0.0381***	**Time**	**0.0286***	Time	0.4193
	Nausea duration (vs. not specified)	**0.0376***	Nausea location (vs. not specified)	0.5801	Nausea severity	0.2399	**Vomiting onset (vs. all day)**	**0.0016***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	**0.0119***	A: abdomen	0.6255			**AM**	**0.0006***		
	B: >0.5–2 h	**0.0077***	B: abdomen + other site	0.6867			**PM**	**0.0023***		
	C: >2–14 h	**0.0020***	C: head	0.3012						
	D: constant	**0.0206***	D: head + other site	0.617						
	E: on and off	0.1004	E: neck/throat/esophagus	0.555						
			F: stomach/stomach + other site	0.711						
RINV Q2	Time	0.3166	Time	0.7172	**Time**	**0.0515**	Time	0.1161	Time	0.0898
	Nausea duration (vs. not specified)	0.0888	**Nausea location (vs. not specified)**	**0.0129***	**Nausea severity**	**0.0102***	**Vomiting onset (vs. all day)**	**0.0020***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0268	A: abdomen	0.2816			**AM**	**0.0013***		
	B: >0.5–2 h	0.0259	B: abdomen + other site	0.9638			**PM**	**0.0014***		
	C: >2–14 h	0.0178	C: head	0.1724						
	D: constant	0.1515	D: Head + other site	0.0696						
	E: on and off	0.3124	E: neck/throat/esophagus	0.5207						
			F: stomach/stomach + other site	**0.0254***						
RINV Q3	**Time**	**0.0212***	Time	0.0929	**Time**	**0.0077***	**Time**	**0.0485***	Time	0.2265
	Nausea duration (vs. not specified)	0.1726	**Nausea location (vs. not specified)**	**0.0453***	Nausea severity	0.2765	**Vomiting onset (vs. all day)**	**0.0025***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.036	A: abdomen	0.1387			**AM**	**0.0012***		
	B: >0.5–2 h	0.3697	B: abdomen + other site	0.8442			**PM**	**0.0026***		
	C: >2–14 h	0.0597	C: head	0.414						
	D: constant	0.3429	D: head + other site	0.4342						
	E: on and off	0.3622	E: neck/throat/esophagus	0.1196						
			F: stomach/stomach + other site	**0.0123***						
RINV Q4	Time	0.1573	Time	0.3429	Time	0.1389	**Time**	**0.0336***	Time	0.2245
	Nausea duration (vs. not specified)	0.1691	Nausea location (vs. not specified)	0.1656	Nausea severity	0.4727	**Vomiting onset (vs. all day)**	**0.0228***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.3894	A: abdomen	0.0826			**AM**	**0.0134***		
	B: >0.5–2 h	0.0398	B: abdomen + other site	0.7722			**PM**	**0.0129***		
	C: >2–14 h	0.0501	C: head	0.6337						
	D: constant	0.4423	D: head + other site	0.8043						
	E: on and off	0.5905	E: neck/throat/esophagus	0.7871						
			F: stomach/stomach + other site	0.7439						
RINV Q5	Time	0.1116	Time	0.5702	Time	0.0938	Time	0.0592	Time	0.1593
	Nausea duration (vs. not specified)	0.1872	Nausea location (vs. not specified)	0.1854	Nausea severity	0.5372	**Vomiting onset (vs. all day)**	**0.0068***	**Vomiting episodes**	**<0.0001***

Table 3 (continued)

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting onset	*p* value	Vomiting episodes	*p* value
	A: 0–0.5 h	0.4232	A: abdomen	0.1835			**AM**	**0.0018***		
	B: >0.5–2 h	0.1205	B: abdomen + other site	0.7672			**PM**	**0.0223***		
	C: >2–14 h	0.2188	C: head	0.2163						
	D: constant	0.8853	D: head + other site	0.6342						
	E: on and off	0.9546	E: neck/throat/esophagus	0.6818						
			F: stomach/stomach + other site	0.9129						
RINV Q6	Time	0.2553	Time	0.5248	Time	0.1506	Time	0.1289	Time	0.2808
	Nausea duration (vs. not specified)	**0.0424***	**Nausea location (vs. not specified)**	**0.0150***	Nausea severity	0.121	Vomiting onset (vs. all day)	<0.0001*	Vomiting episodes	<0.0001*
	A: 0–0.5 h	**0.0074***	A: abdomen	0.0699			AM	<0.0001*		
	B: >0.5–2 h	**0.0642**	B: abdomen + other site	0.5569			PM	<0.0001*		
	C: >2–14 h	**0.0076***	C: head	0.2783						
	D: constant	**0.0318***	**D: head + other site**	**0.0015***						
	E: on and off	0.3289	**E: neck/throat/esophagus**	**0.0128***						
			F: stomach/stomach + other site	**0.0199***						
RINV Q7	Time	0.643	Time	0.5319	Time	0.2978	Time	0.0586	Time	0.0525
	Nausea duration (vs. not specified)	0.1803	**Nausea location (vs. not specified)**	**0.0142***	Nausea severity	0.1976	**Vomiting onset (vs. all day)**	**0.0044***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0949	A: abdomen	0.2194			**AM**	**0.0018***		
	B: >0.5–2 h	0.0221	B: abdomen + other site	0.4995			**PM**	**0.0051***		
	C: >2–14 h	0.0408	**C: head**	**0.0059***						
	D: constant	0.2519	D: head + other site	0.4771						
	E: on and off	0.3029	E: neck/throat/esophagus	0.8584						
			F: stomach/stomach + other site	0.369						
RINV Q8	Time	0.7775	Time	0.6515	Time	0.3343	**Time**	**0.0226***	Time	0.1421
	Nausea duration (vs. not specified)	0.1695	**Nausea location (vs. not specified)**	**0.0483**	Nausea severity	0.3009	**Vomiting onset (vs. all day)**	**0.0127***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0371	A: abdomen	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***						
	D: constant	0.1004	D: head + other site	0.4941						
	E: on and off	0.0834	E: neck/throat/esophagus	0.8708						
			F: stomach/stomach + other site	0.7324						
RINV Q9	Time	0.3631	Time	0.3249	Time	0.7642	Time	0.8456	Time	0.0528
	Nausea duration (vs. not specified)	0.6612	Nausea location (vs. not specified)	0.4624	Nausea severity	0.1139	Vomiting onset (vs. all day)	0.759	**Vomiting episodes**	**<0.0001***
	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						

Table 3 (continued)

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting onset	*p* value	Vomiting episodes	*p* value
	D: constant	0.336	D: head + other site	0.8943						
	E: on and off	0.7704	E: neck/throat/esophagus	0.6272						
			F: stomach/stomach + other site	0.3839						
RINV Q10	Time	0.5385	Time	0.7734	Time	0.0899	Time	0.0848	Time	0.7749
	Nausea duration (vs. not specified)	0.2127	Nausea location (vs. not specified)	0.1283	**Nausea severity**	**0.0152***	**Vomiting onset (vs. all day)**	**0.0071***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0465	A: abdomen	0.349			**AM**	**0.0043***		
	B: >0.5–2 h	0.0223	B: abdomen + other site	0.054			**PM**	**0.0043***		
	C: >2–14 h	0.0305	C: head	0.0539						
	D: constant	0.0994	D: head + other site	0.6773						
	E: on and off	0.183	E: neck/throat/esophagus	0.9768						
			F: stomach/stomach + other site	0.9316						
RINV Q11	Time	0.3257	Time	0.1431	Time	0.696	Time	0.7013	**Time**	**0.0490***
	Nausea duration (vs. not specified)	**0.0201**	**Nausea location (vs. not specified)**	**0.0023**	**Nausea severity**	**0.0044***	**Vomiting onset (vs. all day)**	**0.0004***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	**0.0013***	A: abdomen	0.6761			**AM**	**0.0007***		
	B: >0.5–2 h	**0.0039***	**B: abdomen + other site**	**0.0332***			**PM**	**0.0002***		
	C: >2–14 h	**0.0008***	**C: head**	**0.0374***						
	D: constant	**0.0024***	D: head + other site	0.7497						
	E: on and off	**0.0135***	E: neck/throat/esophagus	0.7483						
			F: stomach/stomach + other site	0.6528						
RINV Q12	Time	0.8756	Time	0.5104	Time	0.2198	Time	0.246	Time	0.2656
	Nausea duration (vs. not specified)	**0.0418**	Nausea location (vs. not specified)	0.0895	**Nausea severity**	**0.0032***			**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	**0.0033***	A: abdomen	0.9147			**Vomiting onset (vs. all day)**	**0.0015***		
	B: >0.5–2 h	**0.0074***	B: abdomen + other site	0.2177			**AM**	**0.0012***		
	C: >2–14 h	**0.0027***	C: head	0.0582			**PM**	**0.0010***		
	D: constant	**0.0101***	D: head + other site	0.9334						
	E: on and off	**0.0422***	E: neck/throat/esophagus	0.8114						
			F: stomach/stomach + other site	0.5724						
RINV Q13	Time	0.9485	Time	0.6785	Time	0.2048	Time	0.2149	Time	0.2399
	Nausea duration (vs. not specified)	0.1052	Nausea location (vs. not specified)	0.1414	**Nausea severity**	**0.0099***	**Vomiting onset (vs. all day)**	**0.0256***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0235	A: abdomen	0.9103			**AM**	**0.0206***		
	B: >0.5–2 h	0.0222	B: abdomen + other site	0.2669			**PM**	**0.0117***		
	C: >2–14 h	0.0059	C: head	0.0619						
	D: constant	0.0344	D: head + other site	0.9846						
	E: on and off	0.1343	E: neck/throat/esophagus	0.5891						

Table 3 (continued)

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting onset	*p* value	Vomiting episodes	*p* value
			F: stomach/stomach + other site	0.8551						
RINV Q14	Time	0.8659	Time	0.4003	Time	0.2824	Time	0.061	Time	0.5579
	Nausea duration (vs. not specified)	0.0882	Nausea location (vs. not specified)	0.0524	**Nausea severity**	**0.0119***	**Vomiting onset (vs. all day)**	**0.0263***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.012	A: abdomen	0.807			**AM**	**0.0173***		
	B: >0.5–2 h	0.017	B: abdomen + other site	0.317			**PM**	**0.0137***		
	C: >2–14 h	0.006	C: head	0.0277						
	D: constant	0.0268	D: head + other site	0.9758						
	E: on and off	0.1076	E: neck/throat/esophagus	0.7125						
			F: stomach/stomach + other site	0.4759						
RINV Q15	Time	0.3491	Time	0.0688	Time	0.7377	Time	0.409	Time	0.0384*
	Nausea duration (vs. not specified)	**0.0344**	**Nausea location (vs. not specified)**	**0.0062***	**Nausea severity**	**0.0094***	**Vomiting onset (vs. all day)**	**<0.0001***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	**0.0021***	A: abdomen	0.9298			**AM**	**<0.0001***		
	B: >0.5–2 h	**0.0060***	B: abdomen + other site	0.117			**PM**	**0.0002***		
	C: >2–14 h	**0.0044***	**C: head**	**0.0060***						
	D: constant	**0.0156***	D: head + other site	0.9997						
	E: on and off	**0.0336***	E: neck/throat/esophagus	0.9612						
			F: stomach/stomach + other site	0.4825						
RINV Q16	Time	0.6182	Time	0.257	Time	0.4407	Time	0.1451	Time	0.6193
	Nausea duration (vs. not specified)	0.0561	**Nausea location (vs. not specified)**	**0.0211***	**Nausea severity**	**0.0133***	**Vomiting onset (vs. all day)**	**0.0015***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0056	A: abdomen	0.8014			**AM**	**0.0010***		
	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***						
	D: constant	0.013	D: head + other site	0.9272						
	E: on and off	0.0551	E: neck/throat/esophagus	0.7443						
			F: stomach/stomach + other site	0.6192						
RINV Q17	Time	0.6174	Time	0.2839	Time	0.4601	Time	0.3968	Time	0.1134
	Nausea duration (vs. not specified)	0.053	Nausea location (vs. not specified)	0.0755	**Nausea severity**	**0.0103***	**Vomiting onset (vs. all day)**	**0.0042***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0062	A: abdomen	0.8877			**AM**	**0.0014***		
	B: >0.5–2 h	0.0102	B: abdomen + other site	0.2346			**PM**	**0.0073***		
	C: >2–14 h	0.0026	C: head	0.0376						
	D: constant	0.0155	D: head + other site	0.8993						
	E: on and off	0.0549	E: neck/throat/esophagus	0.6801						
			F: stomach/stomach + other site	0.8149						
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)

QOL	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)		Nausea location (vs. not specified)				Vomiting onset (vs. all day)			
	A: 0–0.5 h	0.4672	A: abdomen	0.7283			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 (vs. not specified)	0.0905	Nausea location (vs. not specified)	0.0778	Nausea severity	0.3092			**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0433	A: abdomen	0.8885			**Vomiting onset (vs. all day)**	**0.0022***		
	B: >0.5–2 h	0.0245	B: abdomen + other site	0.9998			**AM**	**0.0008***		
	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 (vs. not specified)	0.101	Nausea location (vs. not specified)	0.0563	**Nausea severity**	**0.0055***	**Vomiting onset (vs. all day)**	**0.0013***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.0145	A: abdomen	0.9946			**AM**	**0.0007***		
	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	0.699						

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 variable. Vomiting onset was classified as AM, PM, vs. all day. Vomiting episodes were used as a numeric variable

**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

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 QLQ-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 ± 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_3RA 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

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting episodes	*p* value
C30 physical functioning	**Time**	**<0.0001***	**Time**	**<0.0001***	**Time**	**<0.0001***	**Time**	**<0.0001***
	Nausea duration (vs. not specified)	0.2965	**Nausea location (vs. not specified)**	**<0.0001***	**Nausea severity**	**0.0019***	**Vomiting episodes**	**0.0059***
	A: 0–0.5 h	0.1249	**A: abdomen**	**0.0001***				
	B: >0.5–2 h	0.8592	**B: abdomen + other site**	**0.0487***				
	C: >2–14 h	0.6461	C: head	0.5071				
	D: constant	0.179	D: head + other site	0.2003				
	E: on and off	0.0668	**E: neck/throat/esophagus**	**0.0047***				
			F: stomach/stomach + other site	0.3984				
C30 role functioning	**Time**	**<0.0001***	**Time**	**0.0001***	**Time**	**0.0002***	**Time**	**<0.0001***
	Nausea duration (vs. not specified)	0.4067	**Nausea location (vs. not specified)**	**0.0001***	**Nausea severity**	**0.0018***	Vomiting episodes	0.0991
	A: 0–0.5 h	0.5728	**A: abdomen**	**0.0004***				
	B: >0.5–2 h	0.3602	B: abdomen + other site	0.8531				
	C: >2–14 h	0.8048	**C: head**	**0.0149***				
	D: constant	0.1163	**D: head + other site**	**0.0026***				
	E: on and off	0.1015	**E: neck/throat/esophagus**	**0.0047***				
			F: stomach/stomach + other site	0.3967				
C30 emotional functioning	**Time**	**0.0230***	**Time**	**0.0015***	**Time**	**0.0012***	**Time**	**<0.0001***
	Nausea duration (vs. not specified)	0.1391	Nausea location (vs. not specified)	0.3604	Nausea severity	0.357	**Vomiting episodes**	**0.0012***
	A: 0–0.5 h	0.5173	A: abdomen	0.0652				
	B: >0.5–2 h	0.9728	B: abdomen + other site	0.5117				
	C: >2–14 h	0.1917	C: head	0.7124				
	D: constant	0.3814	D: head + other site	0.9602				
	E: on and off	0.242	E: neck/throat/esophagus	0.6205				
			F: stomach/stomach + other site	0.0981				
C30 cognitive functioning	Time	0.6091	Time	0.7574	Time	0.9815	Time	0.7166
	Nausea duration (vs. not specified)	0.3882	Nausea location (vs. not specified)	0.4028	Nausea severity	0.7082	Vomiting episodes	0.0506
	A: 0–0.5 h	0.9582	A: abdomen	0.2336				
	B: >0.5–2 h	0.7956	B: abdomen + other site	0.2361				
	C: >2–14 h	0.2304	C: head	0.3203				
	D: constant	0.5126	D: head + other site	0.2685				
	E: on and off	0.9363	E: neck/throat/esophagus	0.0169				
			F: stomach/stomach + other site	0.2948				
C30 social functioning	**Time**	**0.0002***	**Time**	**0.0005***	**Time**	**0.0012***	**Time**	**<0.0001***

Table 4 (continued)

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting episodes	*p* value
	Nausea duration (vs. not specified)	0.2951	**Nausea location (vs. not specified)**	**0.0001***	**Nausea severity**	**0.0003***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.2993	**A: abdomen**	**0.0202***				
	B: >0.5–2 h	0.0388	**B: abdomen + other site**	**0.0194***				
	C: >2–14 h	0.1217	C: head	0.7826				
	D: constant	0.0811	D: head + other site	0.1909				
	E: on and off	0.0777	E: neck/throat/esophagus	0.93				
			F: stomach/stomach + other site	0.1589				
C30 global health status	Time	0.8378	Time	0.9706	Time	0.9536	**Time**	**0.0008***
	Nausea duration (vs. not specified)	0.366	Nausea location (vs. not specified)	0.0679	Nausea severity	0.0687	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.3505	A: abdomen	0.0291				
	B: >0.5–2 h	0.4336	B: abdomen + other site	0.0037				
	C: >2–14 h	0.0479	C: head	0.0832				
	D: constant	0.2512	D: head + other site	0.0456				
	E: on and off	0.9203	E: neck/throat/esophagus	0.0058				
			F: stomach/stomach + other site	0.0089				
C30 fatigue	**Time**	**0.0174***	Time	0.2748	Time	0.3209	**Time**	**<0.0001***
	Nausea duration (vs. not specified)	**<0.0001***	**Nausea location (vs. not specified)**	**0.0039***	**Nausea severity**	**<0.0001***	**Vomiting episodes**	**0.0391***
	A: 0–0.5 h	0.0861	A: abdomen	0.168				
	B: >0.5–2 h	0.4482	B: abdomen + other site	0.8558				
	C: >2–14 h	0.0986	C: head	0.4624				
	D: constant	0.596	D: head + other site	0.4598				
	E: on and off	0.0096*	E: neck/throat/esophagus	0.0006*				
			F: stomach/stomach + other site	0.8655				
C30 nausea/vomiting	Time	0.6994	Time	0.99	Time	0.6361	Time	0.3215
	Nausea duration (vs. not specified)	0.4925	Nausea location (vs. not specified)	0.5868	**Nausea severity**	**0.0081***	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.5374	A: abdomen	0.8901				
	B: >0.5–2 h	0.1575	B: abdomen + other site	0.2887				
	C: >2–14 h	0.592	C: head	0.7079				
	D: constant	0.8248	D: head + other site	0.6626				
	E: on and off	0.9696	E: neck/throat/esophagus	0.3193				
			F: stomach/stomach + other site	0.9249				
C30 pain	**Time**	**<0.0001***	**Time**	**<0.0001***	**Time**	**<0.0001***	**Time**	**<0.0001***

Table 4 (continued)

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting episodes	*p* value
	Nausea duration (vs. not specified)	**0.0022***	Nausea location (vs. not specified)	0.0581	Nausea severity	0.2395	**Vomiting episodes**	**0.0003***
	A: 0–0.5 h	**0.0043***	A: abdomen	0.5471				
	B: >0.5–2 h	0.0679	B: abdomen + other site	0.4887				
	C: >2–14 h	0.0697	C: head	0.7601				
	D: constant	0.5526	D: head + other site	0.0654				
	E: on and off	0.5534	E: neck/throat/esophagus	0.2373				
			F: stomach/stomach + other site	0.4312				
C30 dyspnoea	**Time**	0.0238*	Time	0.0746	Time	0.1014	**Time**	**0.0002***
	Nausea duration (vs. not specified)	0.0289*	Nausea location (vs. not specified)	0.7777	Nausea severity	0.6724	Vomiting episodes	0.056
	A: 0–0.5 h	0.0533	A: abdomen	0.2844				
	B: >0.5–2 h	**0.0240***	B: abdomen + other site	0.7088				
	C: >2–14 h	0.4233	C: head	0.7792				
	D: constant	0.4537	D: head + other site	0.2316				
	E: on and off	0.5781	E: neck/throat/esophagus	0.3214				
			F: stomach/stomach + other site	0.0595				
C30 insomnia	Time	0.334	Time	0.4471	Time	0.5785	Time	0.8945
	Nausea duration (vs. not specified)	0.8538	Nausea location (vs. not specified)	0.4747	Nausea severity	0.1222	Vomiting episodes	0.0519
	A: 0–0.5 h	0.7391	A: abdomen	0.4328				
	B: >0.5–2 h	0.9675	B: abdomen + other site	0.8164				
	C: >2–14 h	0.9174	C: head	0.034				
	D: constant	0.4265	D: head + other site	0.4447				
	E: on and off	0.2872	E: neck/throat/esophagus	0.6791				
			F: stomach/stomach + other site	0.2806				
C30 appetite loss	Time	0.9072	Time	0.9724	Time	0.9112	Time	<0.0001*
	Nausea duration (vs. not specified)	0.7789	**Nausea location (vs. not specified)**	**0.0101***	**Nausea severity**	**0.0192***	**Vomiting episodes**	**0.0339***
	A: 0–0.5 h	0.7942	A: abdomen	0.0723				
	B: >0.5–2 h	0.9332	**B: abdomen + other site**	**0.0037***				
	C: >2–14 h	0.2902	C: head	0.6728				
	D: constant	0.5408	D: head + other site	0.9171				
	E: on and off	0.9626	E: neck/throat/esophagus	0.746				
			F: stomach/stomach + other site	0.2979				
C30 constipation	**Time**	**0.0063***	**Time**	**0.0014***	**Time**	**0.0128***	**Time**	**<0.0001***

Table 4 (continued)

QOL	Nausea duration	*p* value	Nausea location	*p* value	Nausea severity	*p* value	Vomiting episodes	*p* value
	Nausea duration (vs. not specified)	**0.0083***	Nausea location (vs. not specified)	0.0686	Nausea severity	0.8853	**Vomiting episodes**	**<0.0001***
	A: 0–0.5 h	0.4771	A: abdomen	0.7857				
	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 (vs. not specified)	0.5727	**Nausea location (vs. not specified)**	**0.0131***	**Nausea severity**	**0.0264***	**Vomiting episodes**	**0.0369***
	A: 0–0.5 h	0.6354	**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**	**0.0010***	**Time**	**0.0041***	Time	0.2192
	Nausea duration (vs. not specified)	0.7986	**Nausea location (vs. not specified)**	**0.0088***	Nausea severity	0.2568	**Vomiting episodes**	**0.0401***
	A: 0–0.5 h	0.9055	**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	**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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