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REVIEW ARTICLE

Radiation-induced nausea and vomiting: a comparison between MASCC/ESMO, ASCO, and NCCN antiemetic guidelines

Erin McKenzie[1] · Pearl Zaki[1] · Srinivas Raman[1] · Robert Olson[2] · Thomas McFarlane[1] · Carlo DeAngelis[1] · Stephanie Chan[1] · William Pidduck[1] · Yasmeen Razvi[1] · Ahmad Bushehri[1] · Edward Chow[1,3]

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Abstract

Purpose Radiation-induced nausea and vomiting (RINV) can affect 50–80% of patients undergoing radiotherapy and negatively impacts quality of life. This review aimed to compare the most recent RINV antiemetic guidelines produced by the Multinational Association for Supportive Care in Cancer (MASCC), the European Society of Clinical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN). Future improvements to the guidelines and the need for further research in RINV were also discussed.

Methods Antiemetic guidelines produced by MASCC/ESMO, ASCO, and NCCN were examined to identify similarities, differences, and inadequacies within the guidelines.

Results Areas of dissension within the guidelines include the addition of dexamethasone to moderate-risk antiemetic regimens, the prophylactic treatment of RINV in the low-risk categories, and the appropriate treatment for breakthrough emesis. The guidelines are in accordance that high-risk radiotherapy regimens should be treated prophylactically with a serotonin receptor antagonist and for those undergoing concurrent chemotherapy and radiotherapy, antiemetic treatment should be prescribed according to the emetic risk associated with their respective chemotherapy regimen. Low- and minimal-risk recommendations are based on low-level evidence and informal consensus.

Conclusion RINV is a frequent and distressing side effect of radiotherapy and requires further research to establish effective antiemetic guidelines and ensure optimal treatment outcomes.

Keywords Nausea and vomiting · Antiemetics · Radiation oncology · Antiemetic guidelines

Introduction

Radiation-induced nausea and vomiting (RINV) is a frequent and distressing side effect of radiotherapy. While as many as 50–80% of patients undergoing radiotherapy experience RINV, under-treatment remains a significant concern [1, 2]. Nausea and vomiting due to cancer treatment can lead to complications such as dehydration, electrolyte imbalance, and malnutrition [3]. Nausea and vomiting also have a negative impact on quality of life (QOL), resulting in emotional distress, inability to carry out daily activities, tiredness, loss of appetite, weakness, and disruption of social and work life [4, 5]. In severe cases, patients suffering from RINV may need to delay or stop radiotherapy, further potentiating poor treatment outcomes.

While little is known about the pathophysiology behind RINV, many believe that the causal factors underlying RINV and chemotherapy-induced nausea and vomiting (CINV) are related [6]. The heterogeneity in irradiated sites and variable effects of radiation on the body make it challenging to identify a causal mechanism for RINV. RINV can occur within 24 h of treatment (acute phase) or within 2–10 days after treatment completion (delayed phase) [7]. Medications known as antiemetics are given either prophylactically or as rescue therapy

✉ Edward Chow
Edward.Chow@sunnybrook.ca

[1] Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

[2] Department of Radiation Oncology, BC Cancer Centre for the North, University of Northern British Columbia, University of British Columbia, Vancouver, BC, Canada

[3] Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada

once an emetic event has occurred. The principal constituent of RINV antiemetic regimens is the 5HT3 serotonin receptor antagonist (5HT3 RA) as it is the most well-studied antiemetic for radiotherapy with a proven record of success [3, 6, 8–12]. Prior to the emergence of evidence highlighting the superiority of 5HT3 RAs, dopamine receptor antagonists (DRAs) were one of the most commonly used antiemetics in practice [3, 13]. Other antiemetics such as dexamethasone (DEX) and neurokinin 1 receptor antagonists (NK1 RA) have proven beneficial in RINV treatment but are not as well substantiated within the literature due to a lack of prospective clinical studies investigating these antiemetics [14–18].

Due to the frequent incidence of RINV, health providers have recognized the importance of guidelines for optimal prevention and treatment of RINV. The present review will focus on four of the most commonly cited organizations that produce antiemetic guidelines including: the Multinational Association for Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) [19–21]. Due to the limited evidence available on RINV and its potentially deleterious effects, this review aimed to compare the recommendations presented by three major antiemetic guidelines and offer suggestions for future research.

Methods

The analysis constitutes a thorough examination of the published antiemetic guidelines for each organization. First, internal changes in each antiemetic guideline, as well as the published studies used to support these changes, were identified. Key randomized controlled trials and other relevant studies were examined to understand the rationale behind guideline recommendations. Next, the selection process and determination of the strength of the guideline recommendations from each organization were analyzed to compare the methodologies utilized. A comparison was performed to identify similarities and differences between each guideline and to discuss factors leading to any dissension. Recent literature describing future directions in RINV research was considered for discussion.

Results

Levels of emetogenic risk

MASCC/ESMO, ASCO, and NCCN utilize a common risk classification that informs health care providers of the typical incidence of RINV reported in certain radiotherapy regimens. This classification is continuously revised with the advent of new evidence and expert consultations. Table 1 shows the level of emetogenic risk associated with various radiotherapy sites that was used to guide the most recent antiemetic updates. This classification is defined by the location of irradiation and is based on evidence from clinical trials and expert opinion in clinical practice.

Table 1 Levels of emetogenic risk for radiotherapy [20]

Risk level	Site of radiation
High (90%)	Total body irradiation
Moderate (30–90%)	Upper abdomen, craniospinal
Low (10–30%)	Brain, head and neck, thorax, pelvis
Minimal (< 10%)	Extremities, breast

Levels of evidence

Each organization has a unique process by which antiemetic guidelines are developed and legitimized. These processes are summarized in Table 2, which compares the criteria used by each organization to obtain consensus and determine the scientific strength of each recommendation.

Generally, each organization performs a preliminary systematic review of the literature from the time of the previous update to the present. The abstracts are then screened by committee members to exclude irrelevant studies. A conference with expert focus groups is held to assess the literature, and discuss the evidence and standard of practice to form a consensus on the recommended antiemetic practice [19–26].

Key updates

Risk classification

All organizations have agreed on the following changes to the emetogenic risk levels for radiotherapy: total nodal irradiation was excluded as this technique is no longer in use, and half body irradiation (HBI) and upper body irradiation (UBI) were combined into upper abdominal irradiation. This change was made as it has been suggested that the upper abdomen is the physiological source of emetic risk for these sites and HBI/UBI are rarely used [10–13]. Craniospinal irradiation was reclassified as moderate risk instead of low risk to account for the inclusion of the upper abdominal region with this technique and the lower thorax region was renamed thorax region. This change in thorax designation was influenced by a publication from The Italian Group for Antiemetic Research, which revealed that the thorax region demonstrated no distinction in emetic risk between upper and lower regions [27].

Table 2 Comparison of strength and evidence of recommendations by organization [22, 23]

	Levels of evidence/scientific confidence	Levels of consensus/grade of recommendation
MASCC	High—Repeated, well-conducted RCTs of appropriate size were available	High—Consensus of more than 2/3 of panelists
	Moderate—At least one RCT supported by well-conducted phase II trials was available	Moderate—Consensus between 1/3 and 2/3 of panelists
	Low—Formal clinical trials at a level less than mentioned above	Low—Consensus of less than 1/3 of panelists
	Very low—Clinical impression only	
	No confidence possible	
ESMO	I—Evidence from at least one large RCT of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCT without heterogeneity	A—Strong evidence for efficacy with substantial clinical benefit, strongly recommended
	II—Small RCTs or large RCTs with suspicion of bias or meta-analyses of such trials with demonstrated heterogeneity	B—Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
	III—Prospective cohort studies	C—Insufficient evidence for efficacy or benefit does not outweigh the risk or disadvantages, optional
	IV—Retrospective cohort studies or case-control studies	D—Moderate evidence against efficacy or for adverse outcome, generally not recommended
	V—Studies without control group, case reports or expert opinion	E—Strong evidence against efficacy or for adverse outcome, never recommended
ASCO	I—Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. RCTs have low false-positive and low false-negative errors (high power)	A—There is evidence of type I or consistent findings from multiple studies of types II–IV
	II—Evidence is obtained from at least one well-designed experimental study. RCTs have high false-positive and/or negative errors (low power)	B—There is evidence of types II–IV, but findings are generally consistent
	III—Evidence is obtained from well-designed, quasi-experimental studies such as non-randomized, controlled, single-group, pre-post, cohort, time, or matched case-control series	C—There is evidence of types II–IV, but findings are inconsistent
	IV—Evidence is from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies	D—There is little or no systematic empirical evidence
	V—Evidence is from case reports and clinical examples	
NCCN	Category I—high level evidence such as RCTs, with uniform consensus	
	Category IIA—lower level evidence, there is uniform consensus	
	Category IIB—lower level evidence, without uniform consensus but no major disagreement	
	Category III—any level of evidence, there is major disagreement	

RCT randomized control trial

European Society for Medical Oncology (ESMO) Guidelines Committee [24]

MASCC/ESMO

Since the 2009 Perugia Consensus Conference, no randomized control trials evaluating RINV antiemetics have been published, resulting in few changes to the 2016 update. As the craniospinal region was reclassified as a moderate-emetic-risk region, the recommended antiemetic treatment for RINV in this region follows the standard treatment for moderate risk, namely prophylaxis with a 5HT3 RA and optional DEX [19]. Previously, the guidelines stated that this area should be treated with 5HT3 RAs for prophylaxis or rescue [26]. This revision is a result of evidence that prophylaxis with a 5HT3 RA for large field vertebral irradiation partially involving the upper abdomen was superior to DRAs or placebo [10–12].

For low- and minimal-emetic-risk categories, treatment options were extended to include DEX or DRAs in addition to 5HT3 RAs. This change is due to the limited evidence demonstrating the superiority of one antiemetic type over another and the variability in sites of irradiation within these risk categories, which may lead to differing responses to antiemetic types due to distinct mechanisms of action. The guidelines specified that DEX should be used to treat cranial irradiation due to the anti-edema activity of corticosteroids and the consensus of the expert panel on standard oncology practice.

ASCO

In the 2011 guidelines by ASCO, the recommended 5HT3 RAs in the prophylaxis of RINV were granisetron,

ondansetron, palonosetron, dolasetron, and tropisetron with a preference for granisetron or ondansetron [25]. Since many 5HT3 RAs have not been studied extensively in a radiation setting, the updated guidelines only recommend using granisetron or ondansetron for prophylaxis of RINV, with the addition of tropisetron for moderate emetic risk [20]. The scheduling of DEX has also been amended to follow the regular course of the 5HT3 RA for the whole radiation treatment in the high-risk category rather than the previously recommended use of DEX for the first five fractions only. The previous 2011 recommendations were based on a study that found the addition of prophylactic DEX to ondansetron during the first 5 days of treatment resulted in better complete control of vomiting and lower average nausea scores over the 15-day study period [14]. These results provided enough support for the expert panel to revise their previous recommendations to suggest its extended use throughout the entire radiation course to ensure effective prophylaxis for the duration of treatment. In the low- and minimal-risk categories, recommendations for treatment now include DEX, 5HT3 RAs, or DRAs as rescue therapy, whereas previously only 5HT3 RAs as rescue or prophylactic therapy for low risk and 5HT3 RAs or DRAs as rescue therapy for minimal risk were recommended. The recent recommendations do not recommend specific antiemetic types as there is limited evidence regarding comparative efficacy for the use of one antiemetic over another in minimal- and low-risk regions and effects may differ based on irradiated site. This change reflecting the use of rescue therapy alone as opposed to rescue or prophylactic therapy for low risk is based on the limited evidence to support the benefits of prophylaxis for low emetic risk regions and the potential harm of prolonged antiemetic use. The guideline does suggest that after the use of rescue therapy, prophylaxis is acceptable for the remainder of treatment to prevent further occurrence. For concomitant chemotherapy and radiation, the new update recommends that after prophylaxis for antineoplastic agents is complete, prophylaxis for the emetic risk related to radiation should be followed thereafter until antineoplastic agents are started again.

NCCN

The most recent guidelines from NCCN were published in 2017 with the latest publication prior to this in 2015. NCCN publishes guidelines more frequently than MASCC/ESMO and ASCO, and due to the short period between these reviews, minimal evidence was identified to guide new updates within the 2017 publication.

Comparison between guidelines

Though the guidelines recommend very similar treatment courses for RINV, differences arise due to the available evidence at the time of publication as well as expert opinion in the consensus groups. Table 3 outlines the antiemetic guidelines for MASCC/ESMO, ASCO, and NCCN.

In the high-risk category, prophylaxis with a 5HT3 RA and DEX is recommended by all organizations. Since no studies investigating DEX for the treatment of RINV in high-risk regions have been published, the decision for each organization to include DEX prophylactically was based on moderate-risk research. NCCN lists the addition of DEX as optional because only a modest benefit with the addition of DEX to 5HT3 RA regimens has been found, although MASCC/ESMO and ASCO postulate that the benefit with DEX is substantial enough to recommend its usage for high-emetic-risk techniques. A study by Wong et al. ($n = 204$) did not find the addition of DEX to ondansetron to significantly increase the proportion of patients with complete control of emesis and nausea during the first 5 days of upper abdominal irradiation (emesis $p = 0.14$; nausea $p = 0.06$), although the addition of DEX was correlated with improved complete control of vomiting over 15 days of radiotherapy ($p = 0.02$) and lower average nausea scores ($p = 0.03$) [14]. A phase III study by Kirkbride et al. assigned 154 moderate-risk patients to receive either DEX or placebo as a prophylactic agent [15]. Although this study did not include 5HT3 RAs, it did show a 70% complete control rate for prophylaxis with DEX as opposed to 49% with placebo ($p = 0.03$) [15]. These findings resulted in the discordance between organizations on whether the prophylaxis of RINV with DEX provides enough benefit to be definitively recommended.

MASCC/ESMO guidelines do not recommend a specific 5HT3 RA or DRA for RINV as there is limited evidence to support the efficacy of one particular antiemetic agent over another. Within the other organizations, the recommended 5HT3 RA is granisetron and ondansetron as they have been the most well-studied in the radiotherapy setting with proven benefits [2, 7, 9–12, 28]. Within the various guidelines, the most commonly recommended DRAs and corticosteroids are prochlorperazine or metoclopramide and DEX, respectively [19, 20].

For moderate risk, prophylaxis with a 5HT3 RA and the optional addition of DEX is recommended in all guidelines. The optional addition of DEX is reflective of the previously mentioned study by Wong et al. ($n = 204$) which showed that the addition of a short course of DEX to the ondansetron regimen displayed a trend of improved complete control of nausea and vomiting in moderate-risk regimens [14]. However, since these findings were not significant, the expert panels of all three organizations determined that a definitive recommendation could not be confidently provided.

Table 3 Comparison between MASCC/ESMO, ASCO, and NCCN antiemetic guidelines [19–21]

Risk category	MASCC/ESMO 2016	ASCO 2017	NCCN 2017
High	Prophylaxis with a 5HT3 RA and DEX	Prophylaxis with a 5HT3 RA (granisetron, ondansetron) and DEX daily	Prophylaxis with a 5HT3 RA (granisetron, ondansetron) and optional DEX daily
Moderate	Prophylaxis with a 5HT3 RA and optional DEX	Prophylaxis with a 5HT3 RA (granisetron, ondansetron, tropisetron) and optional DEX for the first five fractions	Prophylaxis with a 5HT3 RA (granisetron, ondansetron) and optional DEX daily
Low	Prophylaxis or rescue with a 5HT3 RA, DRA or DEX Cranium—prophylaxis or rescue with DEX	Rescue with a 5HT3 RA (granisetron, ondansetron), DRA (prochlorperazine, metoclopramide), or DEX Cranium—rescue with DEX	None
Minimal	Rescue with a 5HT3 RA, DRA or DEX	Rescue with a 5HT3 RA (granisetron, ondansetron), DRA (prochlorperazine, metoclopramide), or DEX	None
Special considerations			
Concomitant chemotherapy	Antiemetic prophylaxis should follow the guidelines for CINV regimens. If emetic risk of RT is higher than that of the concomitant CT, then the risk level of RT must be chosen to tailor the antiemetic treatment.		
Breakthrough emesis	None	None	Patients who experience breakthrough nausea and/or vomiting may be treated with a different class of agent, or with ondansetron or granisetron if they did not receive primary prophylaxis, as is the custom in CINV

CT chemotherapy, *RT* radiotherapy, *5HT3 RA* serotonin receptor antagonist, *DRA* dopamine receptor antagonist, *DEX* dexamethasone, *CINV* chemotherapy-induced nausea and vomiting

ASCO is also the only organization that recommends the usage of tropisetron as a 5HT3 RA in moderate-risk regions. A notable randomized trial by Aass et al. ($n = 23$) on the usage of tropisetron as a prophylactic agent for RINV reported less severe average experience of nausea ($p = 0.03$) and less mean number of emetic events ($p = 0.07$) in the tropisetron arm as opposed to the metoclopramide arm in the moderate-risk category [8]. However, the small sample size and lack of similar validation studies for tropisetron have limited the inclusion of this 5HT3 RA agent by the other organizations in their respective guidelines.

For low and minimal risk, NCCN does not offer any formal recommendations for the treatment of RINV. MASCC/ESMO suggests prophylaxis or rescue with a 5HT3 RA, DRA, or DEX; whereas ASCO suggests using these antiemetics for rescue purposes only. MASCC/ESMO and ASCO both recommend rescue with a 5HT3 RA, DRA, or DEX for minimal risk. The recommendations for low and minimal risk are generally based on expert opinion and standard of practice due to the lack of evidence in these risk categories [19–21].

NCCN is the only organization that provides a recommendation for breakthrough RINV, displayed in Table 3. All organizations recommend following the antiemetic regimen in the CINV guidelines for concomitant chemotherapy and radiotherapy unless the emetic risk of radiation is higher [19–21].

Discussion

Study methodologies

The amount of literature pertaining to RINV is limited and more high-quality research in RINV is necessary to produce consistent and effective guidelines and better outcomes for patients. The variability in RINV study designs limits the generalizability of their results and leads to inconsistencies in RINV antiemetic recommendations.

A systematic review of 25 studies on the use of 5HT3 RAs for RINV concluded that due to the variable methodologies, outcome measurements, and study endpoints, the appropriate dosing and scheduling of 5HT3 RAs could not be precisely determined [29]. Although most studies examined in this review administered 5HT3 RAs throughout the course of radiation, there was some variability in the administration of antiemetics prior to and following radiation [29]. Also, definitions of outcome measurements such as nausea and emesis are not standardized, limiting the validity of trial comparisons. Several patient self-report tools for treatment-induced nausea and vomiting have been developed that address incidence and severity, patient functionality, and quality of life [30]. Some of these tools include the Chemotherapy-Induced Nausea and

Emesis Quality of Life Questionnaire (CINE-QOL), the Functional Living Index-Emesis (FLIE), and the Morrow Assessment of Nausea and Emesis (MANE) [30]. However, these tools may have limitations in terms of clarity, consistency, and validity, and have yet to be widely adopted in a clinical and research context [30]. Economic endpoints are rarely investigated, and more frequent analyses of cost-benefit calculations could lend insight to the benefits of rescue versus prophylaxis, appropriate dosing, and the affordability of the antiemetic types [29, 31, 32]. Further standardization of study methodologies will produce more consistent conclusions in RINV research and strengthen antiemetic guidelines.

Limited recognition of nausea

None of the RINV guidelines discussed in the present report make a distinction between nausea and vomiting in risk level or recommended treatment. Nausea consistently exhibits inferior complete control rates and can be present without vomiting, whereas emesis is almost always associated with prior nausea, suggesting that nausea may occur via different biological mechanisms than emesis [27, 33–35]. This reflects the need for studies to investigate the physiological origins of nausea and determine the type and combination of antiemetic regimen that best addresses this complex symptom. There is also a significant issue with the underreporting of nausea by patients and underestimating of nausea incidence and severity by clinicians in both RINV and CINV [2, 33, 36]. To address underreporting of nausea, more accurate assessments to determine the presence and severity of nausea should be a priority in RINV research. Also, to manage intractable nausea in the delayed phase, the role of nurses and telehealth could be considered as a possible solution in the form of follow up phone calls and frequent assessments for RINV after the termination of treatment. For example, a mixed-methods case study by Stern et al. ($n = 255$) evaluating the use of telehealth for palliative cancer patients reported greater reassurance of caregivers and easier access to symptom management with the intervention, which are results that could potentially be translated for use in post-radiation follow up for RINV [37]. Further investigation of nausea severity in RINV may highlight the importance of addressing nausea independently and effectively within future guidelines and clinical practice.

Risk level assessment

The risk classification for radiotherapy has been defined solely by the location of radiation despite the potential that many other factors may influence the incidence and severity of RINV. Currently, the only accepted individual-level risk factor for RINV is previous or concomitant chemotherapy, although various other potential patient-related factors have been identified for RINV, such as previous alcohol use, gender, age and previous experience of nausea and vomiting [2, 6, 27]. Despite these findings, neither CINV nor RINV guidelines published by MASCC/ESMO, ASCO, and NCCN distinguish treatment recommendations based on individual risk factors identified in the literature, with the exception of age for CINV guidelines [19–21]. In a study by Pirri et al. evaluating 112 chemotherapy and 88 chemoradiation patients, high premorbid/anticipatory emesis, moderately/highly emetogenic chemotherapy, female gender, previous tumor resection, and low pre-treatment role functioning were identified as independent predictors of 77% of treatment-induced nausea and vomiting incidence [38]. Also, a variation of the 5HT3B receptor gene that potentially alters an individual's response to antiemetic treatment has been discovered [39]. Thus, genetic testing could be considered in the future for patients prescribed highly emetogenic radiotherapy regimens. Furthermore, results from a prospective study by Lee et al. have shown that radiation dose can predict radiation-induced acute nausea; however, acute vomiting did not reach significance [40]. Due to the small number of patients ($n = 49$), more research needs to be conducted before these predictors can be validated and implemented [40]. Once individual risk factors for RINV are elucidated, analysis of these determinants could lead to predictive algorithms to detect a patient's risk of RINV [34]. As risk assessment for RINV improves, more effective and individualized recommendations can be developed.

Low- and minimal-risk research

More evidence is needed for low- and minimal-risk categories as there is a paucity of studies that focus on these levels of risk, potentially leading to contradictory guideline recommendations. For example, MASCC/ESMO's antiemetic recommendations for prophylaxis or rescue treatment in low-risk regions were founded upon a high level of consensus, whereas ASCO does not recommend prophylaxis at all [19, 20]. This discrepancy could be due to difference in opinion within the consensus groups or disparity regarding the methodologies used by each organization to rank levels of evidence and form consensus. Additionally, most studies in RINV are conducted with total body irradiation (TBI) or upper abdominal irradiation, which belong to high- and moderate-risk categories, resulting in considerable difficulty when translating results into other risk categories [8, 10–12]. This is particularly problematic for the low-risk category which represents a heterogenous group of patients with respect to the irradiated sites and response to antiemetic treatment. This reflects the need for targeted research in the low- and minimal-risk categories to determine the most effective antiemetic regimens.

New antiemetics

Novel drugs that have been studied in a chemotherapy setting could be beneficial in the determination of more efficacious

treatments for RINV. The standard treatment for RINV is 5HT3 RAs, which have shown great benefit in the acute phase. However, a study by the Italian Group for Antiemetic Research in Radiotherapy noted that the median time to the first episode of vomiting following radiation was 8 days, likely occurring within the delayed phase [27]. Palonosetron is a second-generation 5HT3 RA that has been proven to display higher rates of complete control in the delayed phase for CINV patients with a comparable safety profile to traditional regimens [41–43]. Preliminary studies of palonosetron for combined chemotherapy and radiation have been conducted, showing promising results [43]. In a prospective pilot study conducted at our center, rates of complete control of vomiting in patients receiving oral palonosetron were compared to a historical complete control of 70% with ondansetron [44]. In evaluable patients ($n = 75$), complete control of vomiting was 93.3% in the acute phase and 93.2% in the delayed phase, showing improved control in comparison to ondansetron [44]. In a smaller subset of patients ($n = 14$ acute phase; $n = 13$ delayed phase) with pre-existing emesis, 21.4% ($n = 3$) and 15.4% ($n = 2$) of patients experienced a reduction in the number of emetic episodes in the acute and delayed phases, respectively [45]. This study showed palonosetron to be safe and potentially efficacious for the treatment of RINV in patients with pre-existing nausea and vomiting.

Additionally, olanzapine has shown benefits in the treatment of breakthrough emesis in CINV when prophylaxis with a 5HT3 RA and DEX has failed [46]. Olanzapine is an antipsychotic that antagonizes multiple receptors related to nausea and vomiting in patients [46]. Currently, the NCCN guideline recommends treatment for breakthrough RINV to use any of the antiemetic treatment options listed for CINV including olanzapine, although not all of these agents have not been tested in an RINV setting [21]. More research into the efficacy of olanzapine in the treatment of breakthrough RINV could permit MASCC/ESMO, ASCO, and NCCN to form evidence-based recommendations for the use of this antiemetic. Also, NK1 RAs have been well studied in chemotherapy settings but have yet to be studied extensively in a radiation setting [47]. Studies in a chemotherapy setting have shown benefit to the usage of a 5HT3 RA, DEX, and an NK1 RA together, although this has not been validated in radiotherapy [47]. A study conducted at our center examined the effect of a combination of granisetron and aprepitant for the management of RINV in patients receiving moderately emetogenic radiotherapy for thoracolumbar bone metastases, showing favorable improvements in complete control of nausea and vomiting and few adverse effects [17]. Further well-designed, randomized controlled studies investigating these medications alone or in combination in a radiation setting could result in new and more effective antiemetic protocols.

Guideline implementation

The development of well-founded and consistent guidelines is ineffectual without the proper implementation into standard practice. A study by Dranitsaris et al. ($n = 195$) in CINV found that granisetron prescriptions that followed antiemetic guidelines had better adherence and resulted in decreased severity of acute nausea and substantial cost-savings [32]. Another study by Molassiotis et al. ($n = 102$) in CINV noted that compliance to antiemetic guidelines was 41% for highly emetogenic chemotherapy, 75% for moderate, 43% for low, and 67% for minimal [31]. This study also found that guideline-adherent antiemetic prescriptions resulted in improved CINV outcomes [31]. A study by Dennis et al. reporting on the international patterns of practice in RINV noted that management decisions by physicians in the moderate- and low-risk cases were particularly heterogeneous in adherence to guideline recommendations, ranging from 7% compliance in Hong Kong to 90% in Australia/New Zealand for two moderate-risk cases [1]. This non-adherence to guidelines could result from differing policies in individual institutions and confusion regarding which guidelines should be followed, demonstrating the need for greater consensus between guideline-producing organizations, particularly for moderate- and low-emetic-risk regions. Further studies on patterns of practice and patient outcomes related to guideline compliance will further validate the benefits of antiemetic guideline adherence for optimal treatment of RINV in the clinical setting.

Systems that promote ease of integration of these guidelines are necessary to ensure adherence. Wiki platforms have been suggested for this purpose and are defined by the user's ability to contribute to the content and structure of a given website, allowing for a greater degree of collaboration. One such wiki platform is being considered in Australia to promote wider dissemination of information and allow newly published randomized trials to be flagged and reviewed expeditiously [34]. Dranitsaris et al. illustrated an example of an integrative system in their prospective study that evaluated the implementation of antiemetic guidelines in practice and recognized the benefit of guideline dissemination, opinion leaders, interactive educational workshops, therapeutic reminders, clinical interventions by pharmacists for inappropriate antiemetic prescriptions, and physician audit [32]. With these innovations, more consistent, widespread, and rapidly available guidelines will enable physicians to ensure the best treatment outcomes for patients.

Conclusion

RINV is a debilitating side effect of radiotherapy that is both underreported and understudied. The antiemetic guidelines published by MASCC/ESMO, ASCO, and NCCN reflect the recommended practices for health care professionals in

addressing RINV based on the best available evidence and expert consensus. More research investigating antiemetic dosing and scheduling regimens, potential use of established CINV antiemetics in the radiotherapy setting, and independent-level risk factors for RINV would be beneficial to strengthen the guidelines' recommendations for practice. However, these guidelines are only effective if they are put into practice. There is a necessity for the implementation of systems that promote guideline adherence and aid health care providers to prescribe the optimal RINV antiemetic regimens in order to optimize QOL for patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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