



Patient perceptions of side-effects

## Multinational study exploring patients' perceptions of side-effects induced by chemo-radiotherapy



Christina H. Ruhlmann<sup>a,\*</sup>, Trine Zeeberg Iversen<sup>b</sup>, Meena Okera<sup>c</sup>, Aida Muhic<sup>d</sup>, Gunnar Kristensen<sup>e,f,g</sup>, Petra Feyer<sup>h</sup>, Olfred Hansen<sup>a,i</sup>, Jørn Herrstedt<sup>a,i</sup>

<sup>a</sup> Department of Oncology, Odense University Hospital; <sup>b</sup> Department of Oncology, Copenhagen University Hospital, Herlev, Denmark; <sup>c</sup> Adelaide Cancer Centre, Royal Adelaide Hospital, Australia; <sup>d</sup> The Finsen Centre, Rigshospitalet, Copenhagen, Denmark; <sup>e</sup> Department for Gynecologic Cancer; <sup>f</sup> Institute for Cancer Genetics and Informatics, Oslo University Hospital; <sup>g</sup> Institute for Clinical Medicine, Oslo University, Norway; <sup>h</sup> Department of Radiation Oncology, Vivantes Clinics Neukoelln, Berlin, Germany; and <sup>i</sup> Institute of Clinical Research, University of Southern Denmark, Denmark

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### ABSTRACT

**Purpose:** We aimed to prospectively assess the incidence, severity and patients' perceptions of side-effects induced by radiotherapy and concomitant weekly cisplatin.

**Patients and methods:** This multinational survey included patients with a diagnosis of gynaecological or head and neck cancer scheduled to receive radiotherapy and concomitant weekly cisplatin. Patients completed a questionnaire prior to anti-cancer treatment and after 3 weeks of treatment. Baseline frequency and severity of symptoms were compared to frequency and severity after 3 weeks of treatment, and patients were asked to rank the five most severe symptoms experienced.

**Results:** An increase in the severity as well as in the mean number of symptoms (18 compared to 24) was observed during treatment. Patients ranked 7 of the 10 most feared baseline symptoms as non-physical, whereas 8 of the 10 most feared symptoms after 3 weeks of treatment were physical. Nausea was ranked as the 5th most severe symptom during treatment, despite 98% of patients receiving antiemetic prophylaxis.

**Conclusion:** Patients with head and neck cancer or gynaecological cancer suffer from a number of primarily non-physical symptoms before starting combined chemo-radiotherapy. After 3 weeks of treatment patients score 8 of the 10 most feared symptoms as physical. Future trials focusing on the prevention of side-effects in patients receiving radiotherapy and concomitant chemotherapy are highly warranted.

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The role and significance of supportive care has become increasingly important due to the increased use of multi-modality and multi-targeting antineoplastic treatments. New drug discovery and potential synergism of approved antineoplastic treatment combinations constantly challenge oncologists to provide effective treatment regimens with low side-effect profiles.

Patients' perceptions of physical and non-physical symptoms experienced during the course of chemotherapy were investigated retrospectively by Coates and colleagues in 1983 [1]. These patients, all diagnosed with advanced cancer, ranked the 5 most feared symptoms as: 'vomiting' (1), 'nausea' (2), 'hair loss' (3), 'thought of coming to treatment' (4), and 'length of treatment' (5). The research group repeated the study in 1993, when new supportive care drugs (e.g. antiemetics) had become available [2]. This study, besides from including patients with advanced cancer, also

included patients receiving adjuvant chemotherapy (primarily cyclophosphamide, methotrexate, and fluorouracil (CMF)). The five most severe symptoms were 'nausea' (1), 'tiredness' (2), 'hair loss' (3), 'effect on family' (4), and 'vomiting' (5). Thus, 'nausea' replaced 'vomiting' as the adverse event considered as the most troublesome adverse event by the patients; a finding that was confirmed in 1997 [3]. Furthermore a subsequent study found that nausea has a significantly higher impact on patients' quality of life than vomiting [4].

The patients' own perceptions of side-effects induced by radiotherapy and concomitant chemotherapy have not been properly investigated, but it is well known that patients undergoing combined modality treatment are subjected to more unpleasant and severe acute and long-term side-effects than those receiving radiotherapy or chemotherapy alone [5–7]. Consequently, this study was designed to address three issues; (I) to prospectively compare the incidence and severity of symptoms before and after 3 weeks of radiotherapy and concomitant cisplatin, (II) to assess the patients' perceptions of the symptoms (ranking of symptoms according to

\* Corresponding author at: Department of Oncology, Odense University Hospital, Sdr. Boulevard 29, Entrance 109, DK-5000 Odense C, Denmark.

E-mail address: c.ruhlmann@dadnet.dk (C.H. Ruhlmann).

severity) before and after 3 weeks of treatment, and (III) to explore risk factors for nausea and vomiting.

## Patients and methods

### Study design and patient selection

This prospective, multicentre, observational study to prospectively identify patients' perceptions of side-effects to radiotherapy and concomitant weekly cisplatin was conducted in 6 centres in four countries (Denmark (3), Australia (1), Norway (1), and Germany (1)). Eligible patients were  $\geq 18$  years of age with histologically confirmed cervical-, vulvar-, or head and neck cancer. Patients were chemo- and radiotherapy naïve. Patients were scheduled to receive External Beam Radiation Therapy (EBRT) and concomitant weekly cisplatin 40 mg/m<sup>2</sup>, (in Australia, patients with head and neck cancer received concomitant cisplatin 100 mg/m<sup>2</sup> every third week). EBRT was given as five fractions per week (Mondays through Fridays) in a dose of 1.8–2.0 Gy per fraction and delivered as either Intensity-Modulated Radiation Therapy (IMRT)-technique with 5–7 fields or as box-technique. The patients treated in Danish centres for head and neck cancer in addition received nimorazole (a hypoxic radiosensitizer) 1200 mg/m<sup>2</sup> concomitant to radiotherapy. Women with gynaecological cancer were not allowed to receive brachytherapy during the 3 week study period. Patients were required to be able to read, understand, and complete the study questionnaires themselves. The study was approved by The Danish Data Protection Agency (approval number 2008-41-2929), and reported to the Regional Ethics Committees.

### Assessment methods

The methodology used in this study was an approximation and an extension of the methods applied by Coates and colleagues [1]. Patients were asked to complete a 54 item questionnaire before start of chemo-radiotherapy and after 3 weeks of treatment (hereafter referred to as pre-treatment and post-treatment). Hence, post-treatment questionnaires assessed the side-effects after 15 fractions of EBRT and 3 weekly cycles of cisplatin. The questions represented 37 physical symptoms and 17 non-physical symptoms graded on a 4-point Likert scale ('not at all', 'a little', 'quite a bit', and 'very much'). Patients ranked the five most severe symptoms from most to least severe. The following patient and treatment data were collected: age, gender, diagnosis, radiotherapy and chemotherapy regimens, and antiemetic treatment.

### Statistical analysis

Data were collected on a web-based database. The incidence of symptoms post-treatment compared to pre-treatment was analysed using McNemar's test. The severity of symptoms was analysed using the Wilcoxon matched pairs signed rank test. For this purpose the Likert scale was assigned numeric values as follows: 'not at all' valued 1, increasing to value 4 for the worst grade. The relative severity (patients' ranking) of symptoms was analysed as follows: five points were allocated to the symptom ranked as most severe, decreasing to 1 point for the symptom ranked as 5th. The points allocated to each symptom were then added and divided by the number of patients in the sample, to give an overall score for each symptom. The analysis was performed for both pre- and post-treatment data, and patients' responses were compared according to diagnosis [1]. Prior to data collection it was decided to explore nausea and vomiting data further, referring to the impact of nausea and vomiting on quality of life [4]. Logistic regression (univariable and multiplicative model) was used to analyse the relationship for both nausea and vomiting post-

treatment, with respect to diagnosis, age, use of aprepitant, and nimorazole. Test for interaction and model checking (goodness-of-fit test) were performed for  $P$ -values  $\leq 0.05$ .

## Results

Patient and treatment characteristics are presented in Table 1. A total of 167 patients entered the study and completed the pre-treatment questionnaire. After 3 weeks of treatment, 88% (147 patients) completed the post-treatment questionnaire. Reasons for not completing the second questionnaire were: treatment cancelled (1), questionnaire not handed out (8), questionnaire not returned (8), and undisclosed reasons (3). Antiemetic prophylaxis was prescribed to 98% of patients. A total of 98% received a serotonin receptor antagonist (RA) and 96% a corticosteroid. Fewer patients treated for head and neck cancer received a neurokinin (NK)<sub>1</sub> RA compared with the gynaecological cancer group (29% versus 43%).

The pre-treatment mean number of physical symptoms was 10 (range 0–26) compared to 16 (range 0–33) post-treatment, and the mean number of non-physical symptoms was 8 (range 0–17) both pre- and post-treatment. The frequencies (proportions of patients reporting) of all symptoms pre- and post-treatment are listed in Supplementary Tables 1 and 2 for physical and non-physical symptoms, respectively. In summary, a significant increase in the number of patients reporting a symptom was observed for 32 of the 37 physical symptoms, and for 5 of 17 non-physical symptoms. A significant decrease in the incidence was seen for 4 of 17 non-physical symptoms ('worrying', 'crying', 'concerns about the thought of coming for treatment', and 'concerns about the length of treatment (chemotherapy)'), whereas no decrease was seen for any of the physical symptoms.

A statistically significant increase in the severity of symptoms was observed for 32 of the 37 physical symptoms, and for 5 of 17 non-physical symptoms (Supplementary Tables 1 and 2). This was in accordance with the increase in incidences. A statistically significant decrease in severity was seen for 5 of 17 non-physical

**Table 1**  
Patient and treatment characteristics.

Patients (N)	167
Diagnosis (N)	
Gynaecological cancer	90
Head & neck cancer	77
Age (median)	
All [range 21–78 years]	56
Gynaecological cancer [range 21–78 years]	54
Head & neck cancer [range 41–77 years]	57
Gender, head & neck cancer only (%)	
Female	26
Male	74
Treatment (median)	
Cisplatin dose [range 40–100 mg/m <sup>2</sup> ]	40
Radiation dose [range 50–70 Gy]	64
Radiation dose per fraction [range 1.8–2 Gy]	2
Hypoxic radiosensitizer, head & neck cancer only (%)	
Nimorazole	71
Antiemetic prophylaxis (%)	
Any prophylaxis	98
5-HT <sub>3</sub> RA	98
Corticosteroid	96
NK <sub>1</sub> RA	38
Antiemetic rescue medication (%)	
Dopamine RA	66
Benzodiazepine	14

Abbreviations: 5-HT<sub>3</sub>: serotonin; NK<sub>1</sub>: neurokinin1; RA: receptor antagonist.

symptoms: 'worrying', 'crying', 'concerns about the thought of coming for treatment', 'concerns about the length of treatment (chemotherapy)', and although the number of patients reporting 'concerns about the length of treatment (radiotherapy)' was comparable pre- and post-treatment, a decrease in severity was observed. No decrease in severity was seen for any of the physical symptoms.

The patients' ranking of symptoms, expressed as the relative severity of symptoms, demonstrated that non-physical symptoms account for 7 of the ten most distressing symptoms before treatment (Table 2). 'Concerns about long-term side-effects' remained the most distressing side-effect during treatment, but overall in the post-treatment category, physical symptoms dominated, accounting for 8 of the 10 most distressing side-effects (Table 3). Tables 2 and 3 list the analyses of the ten most distressing symptoms by diagnosis compared with the overall ranking, which is given in the top row of the tables. Items ranked in the top ten sub-analysis, which were not listed in the top ten of the overall analysis, are listed on the right side of the tables. The ranking of the five most distressing symptoms before treatment was quite consistent for the subgroups (head and neck cancer and gynaecological cancer), whereas the ranking during treatment differs clearly according to the incomparable radiation sites. Consistency was found for 'nausea' however. 'Nausea' was ranked as the 6th most distressing symptom for both subgroups (ranked 5th for the overall group), and as indicated in Supplementary Table 1, 'nausea' was experienced by 71% of patients post-treatment compared with 23% pre-treatment. No association was found between 'nausea' and the following variables: diagnosis, age, use of aprepitant, or nimorazole (the latter was only relevant for the head and neck cancer patients). The same analyses were applied to 'vomiting' revealing a significantly higher risk of vomiting for patients treated for head and neck cancer (49%) compared with patients treated for gynaecological cancer (24%;  $P = 0.001$ ). No confounding factors were found when including the pre-specified variables in the multiplicative model, nor was treatment centre found to be a confounding factor.

## Discussion

Patients who receive radiotherapy and concomitant cisplatin experience a substantial number of physical and non-physical symptoms. On average, the number of physical symptoms increased by 60% during treatment (from 10 to 16), whilst the number of non-physical symptoms was identical pre- and post-treatment. Comparing the average number of symptoms reported post-treatment with the findings reported by Coates (19 symptoms) [1], Griffin (20 symptoms) [2], and de Boer-Dennert (13 symptoms) [3], we conclude that the patients treated with combined chemo-radiotherapy are more burdened by side-effects compared with patients receiving chemotherapy alone. The overall strength of the present study compared to the studies just mentioned, includes the pre-treatment assessments, providing more clear information about the impact of the cancer disease (pre-treatment) and the impact of the cancer disease plus the treatment (post-treatment) on patients' experienced symptoms.

The incidence of radiation-site related symptoms correlated with the ranking of severity of the symptoms for both diagnosis groups (Table 3). Before treatment, 'concerns about long-term side-effects', 'concerns about the thought of coming for treatment', 'concerns about the length of treatment (chemotherapy)', 'worrying', and 'concerns about the length of treatment (radiotherapy)' were ranked as the five most troublesome symptoms, whereas during treatment 'concerns about long-term side-effects' remained the most troublesome symptom for the entire group, the other four

above mentioned non-physical symptoms replaced by physical symptoms. The shift in the patients' perceptions of symptoms observed during treatment, where only 2 of the 10 most distressing symptoms were of non-physical origin, may partly be explained by the lower frequency in reporting non-physical symptoms, and hence, the assumption that patients cope better with their situation. However, the overwhelming addition of physical side-effects that have a direct influence on daily living makes it plausible that the non-physical symptoms still are a heavy burden to patients. The one non-physical symptom that patients consistently before and during treatment considered the worst of all symptoms was 'concerns about long-term side-effects'. Given the fact that patients are potentially subjected to severe long-term side-effects, there is a need that nurses and physicians help the patient cope with the risk.

The increase/decrease in severity correlated with the increase/decrease in incidence of all but one symptom. There was no difference (pre- and post-treatment) in the proportion of patients reporting 'concerns about the length of treatment (radiotherapy)', but there was a significant decrease in reported degree of severity.

Some symptoms were reported more frequently post-treatment compared to pre-treatment regardless of diagnosis, e.g. 'feeling tired', 'need to rest', 'lacking appetite', and 'nausea'. In a phase II study prospectively exploring the risk of nausea and vomiting during 5 weeks of fractionated radiotherapy and concomitant cisplatin for gynaecological cancer, 23% of patients were continuously free from nausea [8]. This is in line with the present results as only 29% of patients did not report nausea. In the same study 33% of patients experienced vomiting (defined as a vomit or dry retch separated by at least 1 min) after 3 weeks of treatment, and this compares to 24% in this study. This 9% difference could be explained by the specific focus on nausea and vomiting, the varied data collection methods including a patient diary, and the fact that none of the patients in the phase II study received a NK<sub>1</sub> RA.

Interestingly, a high proportion of patients treated for head and neck cancer reported vomiting (49%), however, when grading the severity of symptoms, only 12% of those who vomited considered vomiting as 'very much'. This explains why the high proportion was not reflected in the patients ranking of severity of symptoms (ranked 14th). Only 29% of head and neck cancer patients received an NK<sub>1</sub> RA, however no association was found between the risk of vomiting and use of a NK<sub>1</sub> RA. In a study by Givens and colleagues, the incidence of severe nausea or vomiting requiring hospitalisation or outpatient intravenous fluids in patients receiving radiotherapy and concomitant chemotherapy was 27%, but no differentiation between nausea and vomiting was made [9]. An even lower percentage (11%) for grade 3–4 nausea or vomiting was reported in a similar study [10]. Although not registered for the present study, the majority of head and neck cancer patients received IMRT, unlike the patients in the studies just mentioned. The inevitable enlargement of low dose areas in IMRT includes dose to the critical structures in relation to the central emetic pathway (i.e. area postrema, nucleus solitaries, and dorsal vagal complex) when treating head and neck cancer. A retrospective analysis in patients treated with IMRT for head and neck cancer (no concomitant chemotherapy) demonstrated a relationship between the risk of nausea and vomiting, and the mean radiation dose to the critical structures in relation to the central emetic pathway. The percentage of patients suffering from any grade (NCI CTCAE Version 2) of nausea or vomiting was 70%, and 36% of patients had grade 2 or more nausea or vomiting [11]. These figures resemble the present findings, bearing in mind that in the present study patients received concomitant cisplatin, and no information on antiemetic treatment was reported for the retrospective study.

**Table 2**  
Patients' ranking of the relative severity of symptoms pre-treatment by diagnosis.

Group (N)	Concerns about long-term side-effects	Concerns about the thought of coming for treatment	Concerns about the length of treatment (CT)	Worrying	Concerns about the length of treatment (RT)	Concerns about having a needle	Feeling pain	Less interest in sex	Feeling weak	Feeling tired	Other symptoms ranked in the top 10 by group (rank)
Entire group (167)	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	
GYN (90)	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>10</b>	<b>7</b>	<b>6</b>	<b>9</b>	11	Urine incontinence ( <b>8</b> )
H&N (77)	<b>1</b>	<b>2</b>	<b>3</b>	<b>6</b>	<b>4</b>	<b>5</b>	<b>8</b>	21	20	19	Trouble swallowing ( <b>7</b> ) Problems with saliva ( <b>9</b> ) Painful swallowing ( <b>10</b> )

Abbreviations: CT: chemotherapy; H&N: head and neck cancer patients; GYN: gynaecological cancer patients; RT: radiotherapy. The ten most distressing symptoms are highlighted in bold.

**Table 3**  
Patients' ranking of the relative severity of symptoms post-treatment by diagnosis.

Group (N)	Concerns about long-term side-effects	Problems with sense of taste	Trouble swallowing	Problems with saliva	Nausea	Painful swallowing	Concerns about the length of treatment (CT)	Diarrhoea	Painful bowel movements	Feeling tired	Other symptoms ranked in the top 10 by group (rank)
Entire group (147)	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	
GYN (78)	<b>1</b>	<b>7</b>	27	25	<b>6</b>	28	<b>4</b>	<b>2</b>	<b>3</b>	<b>5</b>	Difficulty in controlling bowels ( <b>8</b> ) Thought of treatment ( <b>9</b> ) Difficulty sleeping ( <b>10</b> )
H&N (69)	<b>5</b>	<b>4</b>	<b>1</b>	<b>2</b>	<b>6</b>	<b>3</b>	<b>9</b>	19	20	16	Lacking appetite ( <b>7</b> ) Feeling weak ( <b>10</b> ) Concerns about having a needle ( <b>8</b> )

Abbreviations: CT: chemotherapy; H&N: head and neck cancer patients; GYN: gynaecological cancer patients; RT: radiotherapy. The ten most distressing symptoms are highlighted in bold.

The hypoxic radiosensitizer nimorazole is known to induce nausea and vomiting. In a study randomising patients with head and neck cancer between radiotherapy plus nimorazole and radiotherapy plus placebo the risk of nausea and/or vomiting during 5 weeks of fractionated radiotherapy was approximately 21% in the nimorazole group compared to approximately 8% in the placebo group. No information on antiemetic treatment was provided [7]. However, the present study did not show any difference in the risk of vomiting among patients treated for head and neck cancer whether they received concomitant nimorazole or not, and importantly, in the present study patients received cisplatin as well, and IMRT was not applied in the just mentioned study.

The present study differs a lot from previous studies in patients' perceptions of side-effects [1–3]. We included chemotherapy naïve patients with local disease, all patients received radiotherapy, 98% of patients received antiemetic prophylaxis including a serotonin RA, and nausea was ranked by patients as the fifth most severe symptom. In the study by Coates et al. [1] all patients had advanced disease, both chemotherapy naïve- and non-naïve were included, and none of the patients received antiemetic prophylaxis including a serotonin RA. Patients ranked vomiting (1) and nausea (2) [1]. In the second study, 53% of patients had advanced disease and 47% local disease, 82% of the patients received antiemetic prophylaxis (in 33% the antiemetic regimen included a serotonin RA), and patients ranked nausea (2) and vomiting (4) [2]. In the third

study, 91% of patients were chemotherapy naïve, all received antiemetic prophylaxis including a serotonin RA, and patients ranked nausea (1) and vomiting (4) [3]. In conclusion, despite the use of antiemetic prophylaxis in patients receiving chemotherapy alone or combined with radiotherapy, patients are heavily burdened by nausea, and to a lesser extent by vomiting. Also these studies demonstrate the significant prophylactic effect of the serotonin RAs on vomiting and the sparse activity in preventing nausea, thus with the introduction of the serotonin RAs nausea replaced vomiting as one of the most troublesome adverse effect, an observation that was confirmed in the present study.

The impact of nausea is reflected in the need of rescue antiemetic treatment (a percentage of 66% received a dopamine RA as rescue, and 14% received a benzodiazepine). Treatment of breakthrough nausea and/or vomiting during concurrent chemo-radiotherapy is not evidence based, as no randomised double-blind trials have investigated antiemetics in this setting. The multiple receptor targeting antipsychotic drug, olanzapine is emerging as a potent prophylactic and rescue antiemetic, but further evidence is needed to establish its role in chemo-radiation [12].

Treatment with cisplatin is highly emetogenic, and according to guidelines, (e.g. ESMO/MASCC, ASCO, and NCCN antiemetic guidelines), patients should receive antiemetic prophylaxis consisting of a NK<sub>1</sub> RA, a serotonin RA, and a corticosteroid [13]. In our study the cisplatin dose was 40 mg/m<sup>2</sup>, (except from the Australian centre;

$N = 22$ ), and this dose is less emetogenic than the  $\geq 70$  mg/m<sup>2</sup> used in the NK<sub>1</sub> RA phase III trials [14,15]. However, the guidelines do not take the dose of cisplatin into consideration. The efficacy of a two-drug combination (a serotonin RA and a corticosteroid) in preventing vomiting during the first 24 h after administration of cisplatin 20 mg/m<sup>2</sup>, seems to be in the same order as the efficacy of a three-drug antiemetic regimen (adding NK<sub>1</sub> RA) in patients receiving cisplatin  $\geq 70$  mg/m<sup>2</sup> [16–18]. This is why in our study only a minor proportion of the patients received a NK<sub>1</sub> RA as recommended by the guidelines. The risk of radiotherapy induced nausea and vomiting varies depending on the irradiated site and the size of the irradiated field. The emetogenicity of irradiation of the pelvis or head and neck region is categorised as low (the risk of vomiting is 30–60% given no antiemetic prophylaxis), and according to guidelines, patients treated with low emetogenic radiotherapy should receive prophylaxis or rescue with a serotonin RA. However, in concomitant radiochemotherapy the antiemetic prophylaxis should be in accordance to the chemotherapy-related antiemetic guidelines of the corresponding risk category, unless the risk of vomiting is higher with radiotherapy than chemotherapy, which was not the case in the present study.

The study presented demonstrates that the patients' perception of the severity of adverse events, as a tool can be useful for guidance towards relevant areas for further supportive care investigations. Hence, a randomised double blind, placebo controlled trial (NCT 01074697) to compare two antiemetic regimens (a corticosteroid, a serotonin RA, plus a NK<sub>1</sub> RA or placebo) in patients receiving fractionated radiotherapy and concomitant weekly cisplatin has been completed and results are expected to be published later this year.

### Conflict of interest

The authors declare no conflicts of interest.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2015.09.014>.

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