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ORIGINAL ARTICLE

Comparing the patients' subjective experiences of acute side effects during radiotherapy for head and neck cancer with four different patient-reported outcomes questionnaires

Cecilie Holländer-Mieritz[a], Jørgen Johansen[b], Christoffer Johansen[a], Ivan R. Vogelius[a], Claus A. Kristensen[a] and Helle Pappot[a]

[a]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [b]Department of Oncology, Odense University Hospitalet, Odense, Denmark

ABSTRACT

Background: The systematic use of a Patient-Reported Outcome (PRO) as symptom monitoring during cancer treatment and follow-up has the potential to increase symptom awareness, secure timely management of side effects, improve health-related quality of life and improve data quality. This study was conducted to identify the patients' experience during chemoradiotherapy for squamous cell carcinoma of the head and neck (HNSCC) and to investigate how these symptoms correspond with different PRO questionnaires.

Material and methods: Semi-structured interviews on acute side effects were performed until saturation with HNSCC patients treated with high-dose radiotherapy (RT) ± concomitant chemotherapy. The symptoms were thematically grouped in organ classes in accordance with Medical Dictionary for Regulatory Activities (MedDRA). PRO questionnaires validated for patients with HNSCC during RT were identified in the literature and were compared to the patients' symptoms.

Results: Thirteen patients were interviewed. The most frequently mentioned symptoms were oral pain, decreased appetite, dysphagia, dry mouth, fatigue and hoarseness, in order of frequency. A comparison between the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Head and Neck Cancer (EORTC QLQ-H&N35), the Functional Assessment of Cancer Therapy General and Head and Neck (FACT-H&N), the M.D. Anderson Symptom Inventory Head and Neck questionnaire (MDASI-HN), selected items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and the symptoms described by the patients showed that the PROs do not cover the same symptoms, and no specific questionnaire covers all patient's experiences.

Conclusion: We find, that questionnaires applied in the field of PRO among patients with HNSCC undergoing RT may not fully comprise the experiences of patients and we recommend, that experiences of patients must be included in the design of trials involving PRO, in order to decrease the likelihood of missing out reports of acute side effects.

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Introduction

The systematic use of a Patient-Reported Outcome (PRO) as symptom monitoring during cancer treatment and follow-up has the potential to increase symptom awareness, secure timely management of side effects, improve health-related quality of life (HRQoL) and improve data quality. In the setting of medical oncology, Basch et al. demonstrated that the use of PRO compared to usual care during chemotherapy in patients with metastatic solid tumors even may improve survival, however, including a selected patient population [1,2]. In line with these findings, Denis et al. reported improvement in survival in a PRO follow-up program among lung cancer patients compared to usual care [3]. During radiotherapy (RT), the evidence for the use of PRO is limited.

A common treatment for squamous cell carcinoma of the head and neck (HNSCC) is high-dose intensity-modulated radiotherapy (IMRT). There is high-level evidence for improved disease control with accelerated RT and concomitant chemotherapy [4–8]. These intense treatment regimens result in severe acute and late side effects and affected HRQoL even with highly conformal RT [5,9–12]. The standard approach for assessing treatment induced side effect in patients with head and neck cancer, including HNSCC, during and after RT is observer-based scoring systems such as the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (NCI), the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) or in Denmark, the Danish Head and Neck Cancer Group (DAHANCA) toxicity score [13–15]. In 2006, Jensen et al. in collaboration with DAHANCA showed that the objective assessment made by the clinician, using the DAHANCA toxicity score, was insensitive and nonspecific

CONTACT Cecilie Holländer-Mieritz cecilie.hollaender-mieritz@regionh.dk Department of Oncology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen O Denmark

regarding patient-assessed subjective endpoints [16]. In a recent study by Falchook et al., it was demonstrated that observer-based scoring was lower than patient self-reports during chemoradiotherapy in patients with head and neck cancer [17]. In some studies, the use of PRO in the consultation has been associated with improved symptom control, increased supportive care measures and patient satisfaction [18].

Several site-specific PRO questionnaires for head and neck cancer have been published [19,20]. Previously, these PRO questionnaires have been used as outcome measures to show outcomes such as HRQoL for all patients and not as an intervention assessing the individual patient's side effects during RT [20,21]. Further, patients in such trials may not fully reflect the standard patient population with head and neck cancer meaning that reliability is low [2,3].

To address the above-mentioned limitations, we interviewed patients about their experience of symptoms during IMRT for HNSCC.

Furthermore, we compared the patients' symptoms with the symptoms reported in four validated site-specific PRO questionnaires identified through an existing literature review.

Material and methods

Study design

Patient interviews during radiotherapy

We applied semi-structured interviews, which focused on side effects, and conducted such interviews until data saturation was obtained, defined as the point in which no new information was mentioned by three consecutive patients [22]. The study was conducted at the Department of Oncology, Rigshospitalet, University of Copenhagen, Denmark and approved by the Danish Data Protection Agency (File number, VD-2018-140, I-Suite no. 6381). Informed consent was obtained from all individual participants included in the study. Eligibility required age $\geq$18 years, a diagnosis of HNSCC, the initiation but not end of high-dose IMRT, able to read and speak Danish, and acceptance of participation in the study. The interviews took place in conjunction with the patients' pre-scheduled weekly assessment, within a 2-month time frame in the period September 2017–September 2018. Following informed consent, the clinician (CHM) responsible for the study, interviewed patients about their experiences of symptoms during RT. All symptoms mentioned by the patients were noted regardless of frequency or severity. After the patients had explained their symptoms, they were asked if they had experienced any of the 19 symptoms and domains recommended by Chera et al., if not mentioned during the interview [20]. Chera et al. identified 12 head and neck (H&N) specific core symptoms including 2 HRQoL domains and 7 cancer cross-cutting symptoms [20]. The 12 H&N-specific core symptoms and HRQoL domains identified were: swallowing, oral pain, skin changes, dry mouth, dental health, trismus, taste, thick saliva, shoulder disability, hoarseness, social domain and functional domain. The seven cancer cross-cutting symptoms identified were: anorexia, pain/general, nausea/vomiting, anxiety, dyspnea, fatigue and depression [20].

Patients were also asked if they thought it would be useful for them to use a PRO questionnaire during their treatment and how much time they would spend on it per week. The interviews were audio-recorded. The symptoms identified were translated into English. The interviews were analyzed thematically using the Medical Dictionary for Regulatory Activities (MedDRA) [23,24]. Each symptom was grouped in organ classes according to MedDRA. In a consensus process, the research team agreed on the synonym classification of identical symptoms described in different wording, that is, a patient said, 'My voice has its usual quality and strength', this was determined to be equivalent to 'Have you been hoarse?'. If no MedDRA class was applicable, the item was classified as 'others'. When classified according to MedDRA, the 19 symptoms and domains from Chera et al. resulted in 25 MedDRA symptoms. The reason for this is that nausea and vomiting are classified as two separate symptoms; anorexia is classified as weight decreased and decreased appetite; oral pain includes oropharyngeal pain; social domain includes family stress, impaired quality of life, impaired work ability and personal relationship issue; and shoulder disability is included in physical disability.

Site-specific PRO questionnaires for head and neck cancer

Identification of site-specific PRO questionnaires for head and neck cancer has been established following a systematic review by Ojo et al. [19]. The review identified 19 different site-specific PRO questionnaires. In the first phase of the selection, the PRO questionnaires that did not include HNSCC, for example, skin cancer was excluded, as were PRO questionnaires that only included one study. The Auckland quality of life questionnaires was excluded since it could not be identified further in the literature or through internet search. Table 1 presents the six most frequently used PRO questionnaires for patients with HNSCC [19,25–32]. In the next phase, PRO questionnaires that had not been validated on patients with HNSCC during RT was excluded. The remaining site-specific PRO questionnaires that had been validated in previous studies on patients with HNSCC during RT were EORTC QLQ-H&N35 [25], FACT-H&N [27,32] and MDASI-HN [28]. When the US Food and Drug Administration

Table 1. Frequently used site-specific PRO questionnaires for patients with HNSCC.

Instrument	Patient group	Items
EORTC QLQ-H&N35	HNC patients	35
FACT-H&N	HNC patients	39
HNCI	HNC patients	30
HNQOL	HNC patients	20
MDASI-HN	HNC patients	28
UW-QOL	HNC patients	15

EORTC QLQ-H&N35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Head and Neck Cancer module [25]; FACT-H&N, Functional Assessment of Cancer Therapy General and Head and Neck [27]; HNCI, Head and Neck cancer Inventory [29]; HNQOL, University of Michigan Head and neck QoL questionnaire [30]; MDASI-HN, M.D. Anderson Symptom Inventory Head and Neck questionnaire [28]; UW-QOL, University of Washington Quality of Life Questionnaire [31]. Head and neck cancer (HNC).

Table 2. Site-specific PRO questionnaires validated for patients with HNSCC during RT.

Instrument	Items	Scale	Subscales	Time frame	Item library
EORTC QLQ-H&N35 [25]	35	1–4 (*not at all–very much*), and 1–7 (*very poor–excellent*) and yes/no	Multi-item symptoms scales (7 items) and single-item symptom scales (11 items)	Past week	Yes
FACT-H&N [27]	39	0–4 (*not at all–very much*)	G subscale: physical, social/family, emotional and functional domains (27 items) and HN-subscale (12 items)	Past week	No
MDASI-HN [28]	28	0–10 (*not present–as bad as you can imagine*) or (*did not interfere–interfered completely*)	Core items/general symptoms (13 items), interference items/interference with daily life (6 items), and HN-specific items (9 items)	Past 24 h	Yes
PRO-CTCAE HN [36]	33	0–4 (*not at all–very much*) assess the presence/absence, frequency, severity, and/or interfere	18 symptoms (plus optional write in fields)	Past week	Yes

[a]An item library is a database of items that can be selected depending on e.g. treatment type or disease.

Table 3. Characteristics of participating patients.

	Age	Education level[a]	Type of treatment	No. of fractions	Tumor site	Stage
Patient 1	57	Medium	Concomitant chemoradiotherapy	6/33	Tonsil	T2N1M0
Patient 2	61	Short	Concomitant chemoradiotherapy	12/34	Tonsil	T2N1M0
Patient 3	63	Medium	Concomitant chemoradiotherapy	10/34	Tonsil	T1N2bM0
Patient 4	64	Long	Concomitant chemoradiotherapy	12/34	Nasopharynx	T1N2M0
Patient 5	76[b]	Long	Operation and radiotherapy	32/33	Nasal cavity	T3N0M0
Patient 6	51	Medium	Operation and concomitant chemoradiotherapy	2/34	Tonsil	T1N2bM0
Patient 7	71[b]	Short	Radiotherapy	6/34	Base of tongue	T4aN2M0
Patient 8	59	Medium	Concomitant chemoradiotherapy	26/34	Tonsil	T4N1M0
Patient 9	53	Medium	Concomitant chemoradiotherapy	3/34	Tongue	T2N1M0
Patient 10	68	Medium	Radiotherapy	16/33	Larynx	T1aN0M0
Patient 11	45	Short	Radiotherapy	17/34	Tonsil	T1N1M0
Patient 12	47	Short	Concomitant chemoradiotherapy	17/34	Tonsil	T3N3bM0
Patient 13	59[b]	Short	Concomitant chemoradiotherapy	14/34	Tonsil	T3N1M0

[a]Short: Up to 2 years including skilled and unskilled worker; Medium long: over 2 years up to 5 years; Long: over 5 years.
[b]Next of kin attending the interview.

(FDA) suggested the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to be mandatory as an addition to CTCAE scoring in clinical trials, the PRO-CTCAE items from Sandler et al. was added to the above-mentioned sources [33–36]. Sandler et al. examined the content validity of PRO-CTCAE in patients undergoing RT to establish anatomic site-specific item sets including head and neck [36]. In the present study, items from Sandler et al. will be referred to as PRO-CTCAE HN. The selected PRO questionnaires for this study are described in Table 2. The questions from the four PRO questionnaires were grouped according to MedDRA classes.

Results

We conducted 13 individual semi-structured interviews. Seventy-seven percent were male. As is illustrated in Table 3, 4/17 patients declined participation due to lack of time. The patients experienced 10 new symptoms not included in the predefined symptoms derived from Chera et al. These symptoms were constipation, malaise, radiation mucositis, memory impairment, decreased activity, disturbance in attention, nervousness, sleep disorder, analgesia therapy and nutritional supplements (Table 4). In order of frequency, the six most frequently mentioned symptoms were oral pain, decreased appetite, dysphagia, dry mouth, fatigue and hoarseness. With regard to oral pain, this symptom is captured directly in EORTC QLQ-H&N35 and FACT-H&N. General pain is captured by FACT-H&N, MDASI-HN and PRO-CTCAE HN. Decreased appetite is captured by MDASI-HN and PRO-CTCAE HN. However, EORTC QLQ-H&N35 and FACT-H&N questions on this subject are classified as eating disorder. Only the three symptoms dysphagia, dry mouth and hoarseness are captured in all four PRO questionnaires. Fatigue is captured by FACT-H&N, MDASI-HN and PRO-CTCAE HN but would be identified in EORTC QLQ-C30. Constipation and radiation skin injury are only captured by MDASI-HN and PRO-CTCAE HN. No matter the content of these validated questionnaires, patients may have their own description and view on the side effects, which justifies that patients provide their own reasons for specific side effects, the possible treatment or the need for early intervention as illustrated in Figure 1.

When requested on future use of PRO, 12 patients were keen on using an electronic PRO questionnaire weekly during RT. One patient was uncertain if it would be help full, but he was willing to try. The patients were asked about how much time they wanted to spend per week on a PRO questionnaire. The range was from 5 to 30 min, but the majority felt that a maximum 15 min per week was preferable. Social circumstances are represented by different aspects including family stress, impaired quality of life, impaired work ability, personal relationship issue and physical disability. Psychiatric disorders are in the same way represented by the symptoms anxiety, communication disorder, decreased activity, disturbance in attention, disturbance in

Table 4. Symptoms in the PRO questionnaires or described by the patients according to MedDRA classes.

MedDRA system organ class	Symptom	EORTC QLQ-H&N35	FACT-H&N	MDASI-HN	PRO-CTCAE HN	Interviews
Gastrointestinal disorders	Constipation			X	X	X
	Dry mouth[a]	X	X	X	X	X
	Dysphagia[a]	X	X	X	X	X
	Nausea[a]		X	X	X	X
	Oral pain[a]	X	X			X
	Oropharyngeal pain[a]	X	X			X
	Saliva altered[a]	X		X		X
Dental and gingival conditions	Tooth disorder[a]	X		X	X	
	Vomiting[a]			X	X	X
General disorders and administration site conditions	Fatigue[a]		X	X	X	X
	Malaise	X	X			X
	Pain[a]		X	X	X	
Injury, poisoning and procedural complications	Radiation mucositis	X		X	X	X
	Radiation skin injury[a]			X	X	X
Investigations	Weight decreased[a]	X				X
	Weight increased	X				
Metabolism and nutrition disorders	Decreased appetite[a]			X	X	X
	Eating disorder	X	X			
Nervous system disorders	Dizziness				X	
	Dysgeusia/taste altered[a]	X		X	X	X
	Gait distance			X		
	Hypoaesthesia/numbness			X		
	Memory impairment			X		X
	Trismus[a]	X				
Psychiatric disorders	Anxiety[a]		X		X	X
	Communication disorder	X	X			
	Decreased activity			X		X
	Disturbance in attention					X
	Disturbance in sexual arousal	X				
	Dysphonia/hoarseness[a]	X	X	X	X	X
	Food aversion	X				
	Depressed mood/mood altered[a]		X	X	X	X
	Nervousness		X			X
	Sleep disorder		X	X	X	X
	Stress symptoms			X		
Reproductive system and breast disorders	Libido decreased	X	X			
Respiratory, thoracic and mediastinal disorders	Choking	X		X		
	Cough	X			X	
	Smell change	X				
	Dyspnoea[a]		X	X		
Skin and subcutaneous tissue disorders	Cheilitis				X	
Social circumstances	Alcohol use		X			
	Bedridden		X			
	Family stress[a]		X			X
	Feeding tube user	X				
	Impaired quality of life[a]		X			
	Impaired work ability[a]		X	X		X
	Personal relationship issue[a]	X	X	X		
	Physical disability[a]		X		X	X
	Tobacco		X			
Surgical and medical procedures	Analgesia therapy	X				X
	Nutritional supplements	X				X
	Others	X	X			

[a]MedDRA symptoms corresponding to 19 symptoms/domains recommended by Chera et al. for head and neck clinical trials [20].

sexual arousal, depressed mood/mood altered, nervousness, sleep disorder and stress symptoms.

Discussion

Although four PRO questionnaires have been validated for HNSCC patients during RT [19,25,27,28,36], they have different focus and cover different symptoms and may not fully cover the patients' perceptions of acute side effects from RT, which is of highly importance during RT.

The reason for the diversity could be, that some of these measures have been developed as outcome measures such as HRQoL [25,27] and not for the approach, where PRO is the intervention used as an add on to the physician's objective score of side effects [37,38] to give a more complete picture of the patients situation. Only PRO-CTCAE items and MDASI-HN have been developed for patient symptom monitoring [28,33]. With respect to the EORTC questionnaire it is recommended to use EORCT QLQ-C30 in combination with EORTC QLQ-H&N35 [25,26,39], this will explore more general symptoms, similar to some of the other PRO questionnaires. Two detailed reviews on PRO in head and neck cancer have revealed that most questionnaires available for HNSCC during RT have registered PROs at baseline and at completion of RT, not during treatment [19,20]. It is, therefore, recommended that the validity of established PRO questionnaires during the acute treatment phase should be studied [20]. We

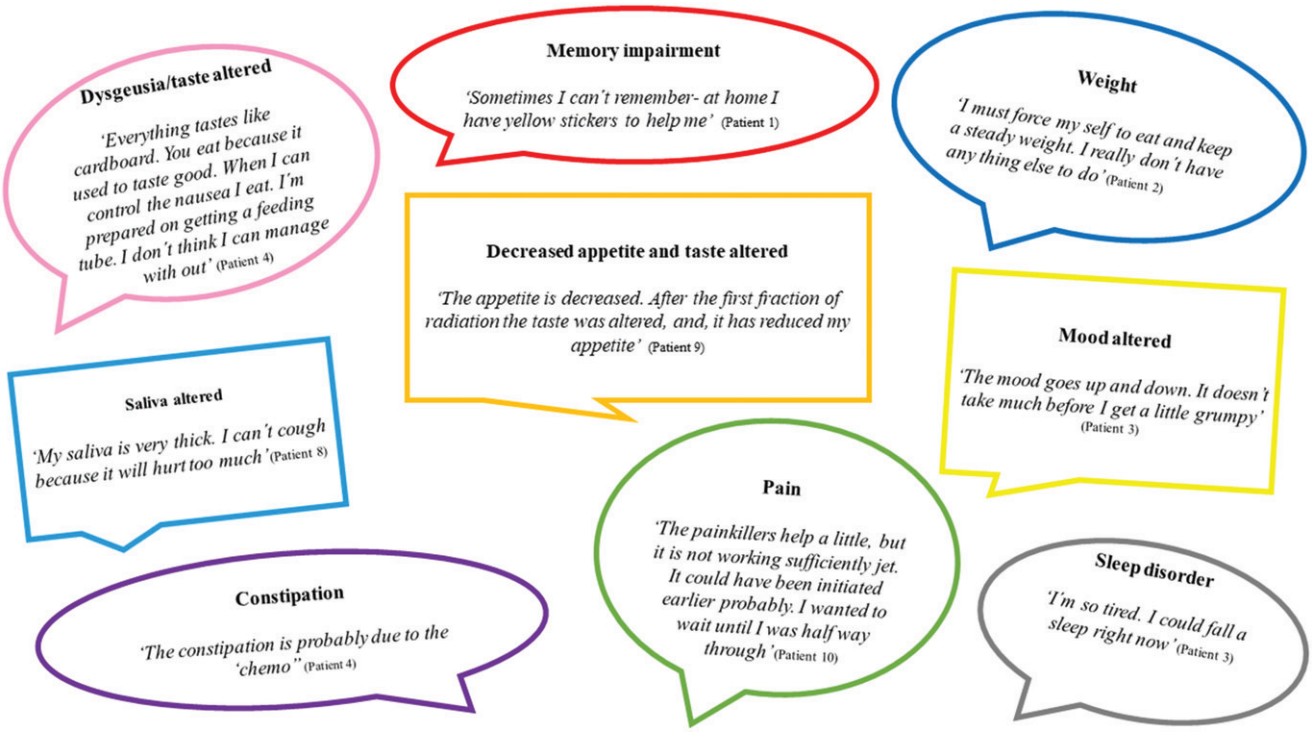

Figure 1. Quotations expressed by current patients with HNSCC.

have identified that different symptoms are covered by different site-specific questionnaires, but not which PRO questionnaire or specific questions that would be optimal for systematic use during RT [18,40]. In this process, involvement of patients may secure that the measures are meaningful for the patients and have a clinical impact on their treatment [41,42].

In this context, one may wonder, if the set of items capturing the most important patient-reported symptoms should be selected with the consideration, that the number of questions exposed to the patients should be kept as low as possible, while still capturing main effects. This approach has recently been performed with success during chemotherapy of metastatic cancer disease [2] and follow-up of lung cancer [3], both studies using schedules including 12 questions and showing significant improvement on survival using PRO [1,3]. In cancer treatment, the combination of PRO as an intervention and as an outcome measure is becoming more frequent. In a study by our group, Taarnhøj et al. demonstrated that there is a high correlation between PRO-CTCAE and QLQ-C30 for the six overlapping symptoms: pain, nausea, vomiting, constipation, diarrhea and fatigue, when applying equal level scales and that for some symptoms, use of questions from one questionnaire can be sufficient [43]. This also indicates that questions from a questionnaire developed for measuring outcome can be used in the setting where PRO is the intervention. Further it is possible, that a free-text field (write-in box) could secure the reporting of symptoms, that can be managed by interventions are not overlooked, but only the PRO-CTCAE has this feature available [40]. The patients interviewed were between fraction number 2 and 32. Acute side effects are expected to emerge and increase during RT. The interviews show that although the majority are in the beginning of treatment they are already experiencing symptoms, suggesting that also early symptoms can be captured by the use of PRO as an add on to the clinical consultation.

PRO is important along the trajectory of cancer treatment. Some of the latest initiatives focus on survivorship, proton therapy and the recurrent setting [44–46]. From a patient's perspective, it seems important that these PRO initiatives share a common trunk, which is recognizable and easy to handle. An international, integrated development process might be warranted with respect to this matter. Additionally, it might seem inevitably to involve patients in clinical trials involving PRO, but nevertheless this is not standard [47,48].

Conclusion

We find, that questionnaires applied in the field of PRO among patients with HNSCC undergoing RT may not fully comprise the experiences of patients and we recommend, that experiences of patients must be included in the design of trials involving PRO, in order to decrease the likelihood of missing out reports of acute side effects.

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Disclosure statement

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ORCID

Cecilie Holländer-Mieritz http://orcid.org/0000-0002-0724-5540
Christoffer Johansen http://orcid.org/0000-0002-4384-206X
Ivan R. Vogelius http://orcid.org/0000-0002-8877-1218
Helle Pappot http://orcid.org/0000-0002-3570-5372

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