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ORIGINAL ARTICLE

Association between late effects assessed by physicians and quality of life reported by head-and-neck cancer survivors

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ABSTRACT

Background: Many survivors of head-and-neck cancer (HNC) suffer from late effects. Their overall quality of life deteriorates during treatment, followed by a slow recovery up to five years after treatment. We examined the association between the severity of physician-assessed late effects and the health-related quality of life (HRQoL) reported by survivors of HNC.

Material and methods: The analysis was based on data collected during follow-up for 136 survivors of cancer in the oral cavity, pharynx, larynx, or salivary glands. Physicians' assessments of dysphagia, xerostomia, fibrosis, and hoarseness, derived from reports to of the Danish Head and Neck Cancer Group database and patient-reported overall quality of life and social, role, emotional, cognitive, and physical functioning reported on the European Organization for Research and Treatment of Cancer questionnaire. Linear regression models were used to examine the association between the severity of each late effect and HRQoL.

Results: Quality of life was decreased among patients with moderate to severe dysphagia compared to patients without dysphagia (−16 points; 95% CI −21;−3). Also role functioning (−20 points; 95% CI −38;−2), emotional functioning (−19 points; 95% CI −34;−4) and social functioning (−27 points; 95% CI −41;−13) decreased compared with patients without dysphagia. Mild dysphagia was also associated with decreased overall quality of life (−12 points; 95% CI −21;−3). Moderate to severe hoarseness was significantly associated with poorer social functioning (−25 points; 95% CI −41;−10). There was no association between fibrosis or xerostomia and HRQoL.

Conclusion: Physician-assessed moderate to severe hoarseness and mild, moderate, or severe dysphagia are associated with clinically relevant decreases in patient-reported quality of life and functioning. Fibrosis and xerostomia of any severity were not associated with changes in any scale of functioning in this study population.

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In view of the improved survival of patients with head-and-neck cancer (HNC) [1], it has become important to investigate their long-term outcomes. Treatment of HNC commonly affects several basic physiological functions, such as swallowing, speech, and salivary function [2]. The highly prevalent short-term effects during treatment decrease over time, but, in some patients, the late effects may be progressive and often irreversible. The physical damage can be accompanied by deterioration in social and physical functioning, as measured on the European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30) [3]. To identify patients who are at risk for impaired health-related quality of life (HRQoL), the late effects adversely associated with HRQoL must be known; however, few studies have addressed the association between the severity of physician-assessed late effects and patient-rated quality of life. Langendijk et al. [4] evaluated the association between physician-rated morbidity of different severity after radiotherapy and patient-assessed HRQoL in 458 Dutch HNC survivors. They found an association between dysphagia and xerostomia and decreased quality of life on various function scales. We examined the same association in the Danish context with a focus on the functioning dimensions of patient-assessed HRQoL in 266 Danish survivors of HNC.

Material and methods

Patient population

The baseline data were obtained from a controlled intervention study, the WebCan Study, of use of patient-reported symptoms and HRQoL outcomes in routine follow-up care [5]. In total, 266 survivors of cancer in the oral cavity, pharynx, larynx, or salivary glands, who were treated with radiotherapy, surgery, chemotherapy, or combinations of these treatments were included in WebCan. To be eligible, survivors had to be recurrence-free, have finished treatment at least six months previously and be attending the regular

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Table 1. DAHANCA morbidity ratings of selected physician-reported late effects.

DAHANCA late effect	Score	Description
Dysphagia	0	None
	1	Slight, normal food
	2	Moderate, soft food
	3	Considerable, liquid food
	4	Severe, despite liquid food
Xerostomia	0	None
	1	Slight
	2	Moderate
	3	Severe
Hoarseness	0	None
	1	Intermittent
	2	Intermittent but daily
	3	Persistent
	4	Total loss of voice
Fibrosis	0	None
	1	Just palpable
	2	Moderate
	3	Severe

follow-up program at the oncology clinic of the Department of Oncology, Herlev Hospital, University of Copenhagen. The WebCan Study has been described in detail elsewhere [5,6]. All procedures in that study were in accordance with the ethical standards of the participating clinical wards, and the study protocol was approved by the Danish Data Protection Agency (No. 2013-41-1857). Informed consent was obtained from all participants in the study.

Exposure

We considered late effects as the exposure. Information on late effects was derived from the Danish Head and Neck Cancer Group (DAHANCA) database. The registrations in the database are based on the oncologists' observations at regular visits. In the five-year follow-up program offered to all patients, physicians prospectively register late effects and score them according to severity at each visit. The late effects used in this study were those that occur at highest incidence according to the literature, on the assumption that a physician will score them objectively [7]. Dysphagia was rated according to ability to eat various consistencies of food (from no problems (0) to severe problems [4]), and xerostomia in relation to intensity (0–3). Hoarseness was rated according to frequency and intensity (0–4) and fibrosis according to palpable changes (0–3). The severity scores were categorized into 0, no problems (reference group); 1, mild problems, and 2–4, moderate to severe problems (Table 1).

Patient-reported health-related quality of life

HRQoL was assessed at the same time as the assessment of the late effects with the EORTC QLQ-C30 [8] using the measures on five functioning scales and overall quality of life. This questionnaire is a valid, reliable measure of HRQoL for patients with cancer. It is used widely for various types of cancer and reflects the multi-dimensionality of the HRQoL construct [8]. The questionnaire contains five functional scales: physical functioning (five items), role functioning (two items), emotional functioning (four items), cognitive functioning (two items), social functioning (two items) and global quality of life (two items). Further, the questionnaire includes nine symptoms scales, which are not evaluated in this study. High scores on the functional scales and the global quality of life scale indicate a high level of functioning. In accordance with the guidelines, the scale scores are linearly transformed to a number between 0 and 100, with 100 representing maximum functioning [8].

Covariates

Clinical information on tumor site and stage, treatment modalities and human papillomavirus (HPV) status were derived from the DAHANCA database [9]. Tumor sites were divided into HPV-associated and others. Stage of disease was defined according to the UICC TNM classification [10] and categorized into early (stages I and II) and advanced (stages III and IV). The five treatment modalities used were: concurrent chemoradiation, radiotherapy and surgery, chemoradiation and surgery, radiation only, and surgery only.

Cohabitation, smoking habit, and level of education were obtained from a self-reported study-specific questionnaire. As cohabitation is considered an indicator of social support, it was categorized into living with a partner (married or cohabitating) or living alone (single, divorced or widowed). Smoking was classified as never, former, and current. In relation to length of education, participants born before 1958 had only seven years of compulsory schooling, while schooling was compulsory for nine years after 1958. Length of education was therefore grouped into short (seven or nine years), medium (8–12 or 10–12 years) and long ($>$12 years) according to the age of the participant.

Information on comorbid conditions was extracted from the Danish National Patient Register, which contains data on all hospitalizations in Denmark since 1977 and all outpatient visits since 1994 for both somatic and psychiatric diseases [11]. Diagnoses were coded according to the International Classification of Diseases, 10th revision (ICD-10), categorized according to the Charlson Comorbidity Index and grouped into scores of 0 (none), 1–2 and $\geq$3. The Charlson Comorbidity Index, which comprises 19 selected conditions scored by severity, was cumulated from 10 years before diagnosis to the time of the baseline assessment [12].

Statistical analysis

Linear regressions models were used to determine the associations between physician-assessed late effects and patient-reported HRQoL. The analyses were adjusted for sex, age, level of education, cohabitation status, time since diagnosis, smoking habits, comorbidity, tumor site, stage of disease, treatment modality, and HPV status. We used quantile–quantile plots to determine that the dependent variables were normally distributed. Information on outcomes was missing for many of the patients with only 136 patients with scores on all four late effects, 14 patients with 1–3 missing scores and 116 with all scores missing. Thus, data from 136 patients could be included in the analysis. Further, as some of the

covariate values were missing, data from 114 participants with physician-assessed dysphagia, 113 with hoarseness, 111 with fibrosis and 114 with xerostomia were included in the final linear regression models.

Results

Of the 136 participants with full data, most were male (77%), married (76%) and had medium (38%) or higher education (42%). In addition, most were non-smokers (22% were never and 68% were former smokers); 63% had no comorbid conditions, while 23% had a Charlson Comorbidity score of 1–2, and 14% had a score ≥3 (Table 2).

Associations between late effects and health-related quality of life

The numbers of late effects by severity as assessed by physicians are shown in Table 3.

Overall quality of life was decreased among patients with all severities of dysphagia in both crude and adjusted analyses (Table 4). Role functioning was decreased with 20 points (95% CI −38;−2), emotional functioning with 19 points (95% CI −34;−4) and social functioning with 27 points (95% CI −41;−13) among patients with moderate to severe dysphagia compared to patients without dysphagia.

Physical functioning was lower in patients with moderate to severe hoarseness compared to patients without hoarseness in crude analyses (−17 points; 95% CI −28;−7). In addition, role functioning decreased with 23 points (95% CI −39;−7) and social functioning was 31 points (95% CI −44;−19) lower in the same group of patients (Table 4). Only the association with social functioning remained statistically significant in the adjusted analyses (−25 points; 95% CI −41;−10).

No significant associations were found between fibrosis and xerostomia and any functioning scale.

In an attrition evaluation we compared sociodemographic factors and disease- or treatment-related variables between participants in the full dataset ($n = 266$) and those included in the analyses ($n = 136$) we found no statistically significant differences. Similarly, there were no differences between the total sample of patients and the 136 patients included in the analyses on mean values of HRQoL (data not shown).

Table 2. Sociodemographic and treatment-related characteristics of 136 HNC survivors.

Variable	n (%)
Sex	
Male	105 (77)
Female	31 (23)
Age (years)	
Range	41–90
Mean	63
<50	7 (5)
50–59	59 (43)
60–69	54 (40)
70–79	12 (9)
>80	4 (3)
Civil status	
Married or cohabitating	103 (76)
Single, divorced or widowed	33 (24)
Education	
Short	22 (16)
Medium	51 (38)
Higher	57 (42)
Other/unknown	6 (4)
Smoking	
Never	30 (22)
Former	92 (68)
Current	14 (10)
Charlson Comorbidity Index	
0	85 (63)
1–2	32 (23)
≥3	19 (14)
Tumor site	
HPV-related cancers[a]	100 (74)
Others[b]	36 (26)
Disease stage	
Early	47 (34)
Advanced	88 (65)
Unknown	1 (1)
Treatment	
Concurrent chemoradiation	75 (55)
Radiation and surgery	14 (10)
Chemotherapy, radiation and surgery	2 (2)
Radiation only	37 (27)
Surgery only	8 (6)
Time since diagnosis (months)	
Mean	21
Range	6–140
6–12	26 (19)
>12–18	45 (33)
>18–24	28 (21)
>24	37 (27)

[a]Cancers in oropharynx and oral cavity; [b]Cancers in glottis larynx, other larynx, hypopharynx, salivary glands and lymph nodes of head, neck or face.

Table 3. Frequency of physician-observed late effects according to DAHANCA-recorded severity in 266 HNC survivors.

	n (%)			
DAHANCA score	Dysphagia	Xerostomia	Hoarseness	Fibrosis
No symptoms	79 (30)	25 (9)	102 (38)	61 (23)
Mild	56 (21)	82 (31)	20 (8)	42 (16)
Moderate–severe	12 (4)	32 (12)	16 (6)	41 (15)
Missing	119 (45)	127 (48)	128 (48)	122 (46)

Discussion

In this cross-sectional study with comprehensive clinical, sociodemographic and lifestyle data, we found a statistically significant association between physician-assessed dysphagia of any severity and clinically relevant, lower patient-reported overall quality of life. Statistically significant associations were also found between moderate to severe dysphagia and emotional functioning, social functioning, and role functioning, even after adjustment for important confounders and mediators. Moderate to severe hoarseness was associated with poorer social functioning; however, the poorer physical and role functioning observed in these patients was attributable to differences in sociodemographic factors, lifestyle, the cancer, or its treatment. The associations with poorer functioning were found even though the population consisted of long-term survivors who had high baseline HRQoL [6]. Previous research has also discussed how to interpret the clinical meaning of HRQoL assessments and a difference of 10 points in the EORTC QLQ-C30 is considered a moderate clinically meaningful change for patients [13]. Most of the statistically

Table 4. Associations between moderate to severe late effects and EORTC QLQ-C30 functioning scales in HNC survivors up to 21 months after treatment.

		Hoarseness ($n = 113$)				Dysphagia ($n = 114$)			
		Crude β (95% CI)		Adjusted β[a] (95% CI)		Crude β (95% CI)		Adjusted β[a] (95% CI)	
	Mean[b]	Mild[c]	Moderate–severe[c]	Mild[c]	Moderate–severe[c]	Mild[c]	Moderate–severe[c]	Mild[c]	Moderate–severe[c]
Overall quality of life	76	−7 (−19;5)	**−15 (−30;0)**	−7 (−20;5)	−14 (−32;4)	**−13 (−21;−4)**	**−22 (−38;−7)**	**−12 (−21;−3)**	**−16 (−21;−3)**
Physical functioning	91	−1 (−10;7)	**−17 (−28;−7)**	1 (−8;9)	−12 (−24;1)	−4 (−11;3)	**−18 (−30;−6)**	−1 (−7;6)	−11 (−24;1)
Role functioning	86	2 (−11;15)	**−23 (−39;−7)**	3 (−10;16)	−15 (−34;4)	−4 (−14;6)	**−26 (−44;−8)**	0 (−10;10)	**−20 (−38;−2)**
Emotional functioning	82	−3 (−14;7)	−12 (−26;2)	−3 (−14;8)	−12 (−28;4)	−6 (−14;1)	**−21 (−35;−7)**	−5 (−13;3)	**−19 (−34;−4)**
Cognitive functioning	85	−1 (−11;9)	−8 (−21;4)	−1 (−11;9)	−5 (−20;9)	−3 (−10;4)	−2 (−15;12)	−2 (−9;6)	1 (−13;15)
Social functioning	88	−2 (−12;8)	**−31 (−44;−19)**	−3 (−14;7)	**−25 (−41;−10)**	−6 (−14;2)	**−30 (−44;−16)**	−3 (−11;5)	**−27 (−41;−13)**
		Fibrosis ($n = 111$)				Xerostomia ($n = 114$)			
		Crude β (95% CI)		Adjusted β[a] (95% CI)		Crude β (95% CI)		Adjusted β[a] (95% CI)	
	Mean[b]	Mild[c]	Moderate–severe[c]	Mild[c]	Moderate–severe[c]	Mild[c]	Moderate–severe[c]	Mild[c]	Moderate–severe[c]
Overall quality of life	76	3 (−7;12)	−10 (−21;1)	5 (−5;15)	−11 (−23;1)	−5 (−18;7)	−10 (−25;4)	−9 (−22;5)	**−15 (−29;0)**
Physical functioning	91	0 (−7;8)	−4 (−12;4)	1 (−6;9)	−2 (−11;6)	2 (−7;11)	−2 (−13;8)	2 (−8;11)	−1 (−12;10)
Role functioning	86	−2 (−13;9)	−8 (−20;4)	2 (−9;13)	−3 (−16;10)	0 (−14;14)	−3 (−19;14)	1 (−13;15)	0 (−17;16)
Emotional functioning	82	−1 (−9;8)	−3 (−13;7)	−1 (−10;8)	−4 (−15;7)	0 (−13;13)	3 (−8;15)	2 (−9;14)	−2 (−16;11)
Cognitive functioning	85	−4 (−13;4)	−2 (−11;7)	−7 (−15;2)	−4 (−14;6)	−3 (−13;7)	−4 (−15;8)	−3 (−14;8)	−5 (−17;7)
Social functioning	88	−5 (−14;4)	7 (−17;3)	−2 (−12;7)	−5 (−16;6)	1 (−10;12)	−11 (−24;1)	3 (−8;14)	−11 (−24;1)

[a]Adjusted for sex, age, education, cohabitation status, time since diagnosis, smoking habits, comorbidity, tumor site, stage of disease, treatment modality, and HPV status; [b]Among the 136 patients with full data; [c]In comparison with reference group (no problems).
Mild has a score of 1 on the DAHANCA scoring sheet, and moderate–severe has scores of 2, 3 and 4. The results in bold are significant ($p \leq 0.05$).

significantly results for dysphagia and hoarseness are considerably higher than this 10-point threshold and this underscores the relevance of HRQoL questionnaires in clinical practice and in the years after treatment has ended, as even survivors with high baseline HRQoL may have reduced HRQoL after treatment.

Improvements in overall HRQoL are observed in HNC patients over time [14,15]; however, there is a tendency to deterioration, especially in physical and social functioning, on the scales measured by the EORTC QLQ-C30 years after treatment has ended [3]. Our aim was to determine whether some late effects particularly adversely affect HRQoL in order to identify patients at risk. Jensen et al. [16] examined the relation between physician- and patient-rated late effects in relation to HRQoL in 116 HNC patients two years after surgery or radiotherapy. Although the authors reported low sensitivity, they found a statistically significant negative correlation between physician-assessed dysphagia, fibrosis and hoarseness and one or more of the function scales in the EORTC QLQ-C30 in a second analysis. Langendijk et al. [4] evaluated the association between different severities of physician-assessed morbidity after radiotherapy and patient-reported HRQoL in 425 patients six, 12, 18 and 24 months after treatment for HNC and found that dysphagia and xerostomia were statistically significant associated with decreased patient-reported HRQoL. Although xerostomia was reported most frequently, HRQoL was affected more by dysphagia. In our patients, a mean of 21 months after the end of treatment, xerostomia and fibrosis were the most frequently reported late effects. Although dysphagia and hoarseness were less frequent, they were statistically significantly associated with patient functioning. All three studies point to the conclusion that dysphagia in particular affects the quality of life of HNC patients. In the present study, the data were collected for patients who were between six months and five years after diagnosis; although we adjusted for time since diagnosis, residual confounding might have been present due to the broad time categories used.

We did not find that xerostomia was associated with HRQoL, even though the association between xerostomia and low HRQoL has been well established [4,17]. Jellema et al. [17] investigated the association between physician-rated xerostomia and the function scales in the EORTC QLQ-C30 in 288 Dutch patients with HNC and found decreases in all scales except emotional functioning with increasing severity of xerostomia two years after treatment. Neither the study of Jensen et al. [16] nor this study indicates an association.

The results regarding hoarseness and HRQoL vary. Jensen et al. [16] found, in line with our results, an association between hoarseness, physical functioning and social functioning in 116 HNC patients two years after treatment, whereas Langendijk et al. [4] found no association with any function scales in the EORTC QLQ-C30. Voice problems may affect relationships with friends and family [18], which may explain the associations with social and role functioning observed in the present study.

One of the strengths of this study is the detailed information on diagnosis, stage of disease, treatment modality and HPV status from the medical files and the DAHANCA database. However, we had only full data on slightly more than half of all WebCan patients. This is a major limitation in the study, which resulted in loss of statistical power in the analyses and may have had an impact on the study results. Attrition analyses indicated that no descriptive differences were present between the total sample and those included in the analyses and further, that the mean HRQoL estimates were similar. The 116 patients with no scores may have had no problems, or the physician was unable to register their problems, and the 14 patients for whom some scores were missing may not have had a problem in those fields for which data were missing. These conjectures cannot be investigated further, but they may have resulted in underestimates of the numbers of patients with late effects in this study.

The severity of late effects is rated by physicians during outpatient visits. As reported by Jensen et al. [7], the ratings

in clinics are often the result of a consensus among clinicians and are not always validated against objective endpoints. Assessments of late effects are therefore based on the patient's history and the physician's observations. Other studies [16,19] have showed that objective endpoints of a physician-assessed scoring system, such as the DAHANCA, are correlated to only a limited degree with HRQoL, suggesting that an observer-based scoring system might underestimate patient complaints. However, in our study some of the observed late effects were significantly related to patient-reported HRQoL. From a clinical perspective, it is important to be aware of the difference between physician- and patient-reported data in order to avoid underestimating the importance of late effects. Physicians' assessments of late effects reflect a synthesis of objective findings, pathophysiological changes, and interpretation of the patient's report during a visit, while patient reports describe health status and subjective complaints [19,20].

Future research should be directed to understanding whether other late effects of different severity also affect HRQoL and whether the number or combinations of late effects are associated with HRQoL, in order to increase the accuracy of patient assessments. This would require a larger study population and should ideally involve multiple centers. Such studies should be stratified on tumor site and treatment modality and could be complemented by assessments of coping, anxiety, depression, and pretreatment values, as these factors are likely to be important in a long-term perspective [3,21,22]. Such findings would nuance information about associations with HRQoL and would provide a guideline for identifying patients who need supportive care or extra attention after treatment [23,24]. For example, HNC survivors returning to work should have an accurate evaluation of the individual impact of their late effects on their functional and psychological abilities. In this evaluation important factors such as age, working demands, psychological resources, and social support must be included in order to evaluate whether they can return to their previous jobs with full or diminished capacity or might have to be retrained or shifted to another job [25].

Conclusion

In this population of HNC survivors, we found clinically relevant associations between physician-assessed hoarseness and dysphagia of differing severity and HRQoL. These results were found in a study population with a high baseline HRQoL and after adjustments for important confounders and mediators. It was also possible to demonstrate an association between mild dysphagia and lower overall quality of life. In daily clinical practice, it is important to identify survivors who experience late effects that strongly influence their HRQoL, so that rehabilitation can be targeted appropriately and HRQoL can be sustained at an acceptable level.

Disclosure statement

No potential conflict of interest was reported by the authors.

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