European Archives of Oto-Rhino-Laryngology (2019) 276:3495–3505
https://doi.org/10.1007/s00405-019-05630-2

HEAD AND NECK

EORTC Quality of Life Questionnaire Head and Neck (H&N)-35 scores from H&N squamous cell carcinoma patients obtained at diagnosis and at 6, 9 and 12 months following diagnosis predict 10-year overall survival

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Received: 12 April 2019 / Accepted: 1 September 2019 / Published online: 16 September 2019

Abstract

Purpose To study the 10-year overall survival predictions, and mechanisms behind, of head and neck (HN) quality of life (QoL) scores obtained at diagnosis and 6, 9, and 12 months following diagnosis in a cohort of HN squamous cell carcinoma (HNSCC) patients.

Methods Consecutive HNSCC patients ($N = 109$) subjected to standard workup and treatment self-reported their QoL measured by the EORTC Quality of Life Questionnaire (QLQ) H&N-35 between November 2002 and June 2005. Each QoL index was calculated and additionally aggregated to one sum score. The included patients were at diagnosis younger than 78 years, judged adequately cognitive functioning, and scheduled for curative treatment. Self-reported smoking, alcohol consumption, and socio-demographic information were registered. Twenty-two patients were high-risk (hr)-HPV DNA tumor positive. If the treatment goal was changed to palliative, no new QoL information was collected. All living patients were followed until 10 years after diagnosis.

Results Median survival was 105 months. Significant overall survival predictions were found from the EORTC H&N-35 QLQ sum scores continuously measured at diagnosis ($p = 0.006$) and obtained at 6 ($p = 0.02$), 9 ($p = 0.002$) and 12 ($p = 0.05$) months. Lower QoL predicted lower overall survival. These sum score survival predictions were in part independent of TNM stage, hr-HPV status, gender, age, alcohol and smoking status. The indices "pain", "swallowing", "social eating", and "feeling ill" were predictive of survival at 3 out of 4 measuring points (diagnosis, 6, 9 and 12 months) in univariate analyses.

Conclusion EORTC H&N-35 QLQ scores at diagnosis and throughout the first year thereafter harbor prognostic power.

Keywords Head and neck neoplasms · Quality of life · Prognosis · Human papilloma virus

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Introduction

Quality of Life (QoL) has an inherent meaning to most people. Presence of disease and treatment can alter one's own perception of QoL. QoL questionnaires have been designed to describe and measure these issues [1]. In head and neck cancer (HNC) patients, this is considered of special importance, as the disease and its treatment may disrupt core aspects of life [2]. Consequently, a substantial number of investigations have been conducted evaluating HN QoL issues among HNC patients before, following, and after treatment [3]. Additionally, HN QoL scores have been shown to be associated with survival in HNC patients [4, 5]. A review by van Nieuwenhuizen et al. evaluating the present literature regarding the prognostic role of QoL responses from HNC patients [4], showed strong evidence for a survival prediction from the general QoL indices "physical function" and "global QoL/health", whereas the evidence was insufficient for most other QoL domains. The authors concluded that more high-quality studies with a longitudinal design were warranted. The available publications vary significantly methodologically with regard to questionnaires applied for the assessment of QoL, the timing of assessment during the clinical pathway, cohort characteristics and size, as well as applied statistics. This further emphasizes the need of more studies [4, 5].

Based on the present cohort of HNC patients, we have previously shown that general and HN QoL scores obtained at the time of diagnosis predicted 5-year overall survival [6]. This association was independent of socio-demographic, clinical and psychological characteristics, health behaviors, as well as comorbidity. The present paper aims to re-evaluate the prognostic effect of HN QoL data obtained at the time of diagnosis with an extended observation time to 10 years. Additionally, the prognostic importance of HN QoL data obtained at 6, 9, and 12 months following diagnosis will be evaluated. The latter time points represent a period where active treatment has been completed, whilst the disease and its treatment still heavily affect patients. To what extent HN QoL scores during this period of the clinical pathway predict prognosis, is not known in detail and should be of interest.

When the present cohort was included, diagnosed, and treated, information regarding high-risk human papilloma virus (hr-HPV) status in tumor was not recognized as important. During the last decades hr-HPV infections have been attributed as a causative agent in particular for oropharyngeal squamous cell carcinoma (SCC) patients [7]. Hr-HPV-positive oropharyngeal SCC patients seem to be different from the traditional HNC patients, i.e., they are younger, healthier, and carry a more favorable prognosis than the HPV-negative counterparts do [8, 9].

We have found it pertinent to evaluate the survival predictions from HN QoL scores obtained at diagnosis and the following year adjusted by both patient and tumor variables, including hr-HPV status.

Materials and methods

Patients

In the period from November 2002 to June 2005 patients below 78 years of age, with adequate cognitive function and a new HNSCC diagnosis, scheduled for curative treatment were asked to participate in the study. The patients were required to answer the questionnaire intelligibly as judged by the primary interviewer (AKHAa). In addition, one of the investigators (HJAa) judged the medical (mental) condition of each patient. If failure in one or both of the above-mentioned evaluations, the patient was not included to the study. One hundred and eleven patients were approached and judged fit for the study, of which five refused to participate. At least 80% of the admitted patients to our institution with newly diagnosed HNSCC were evaluated in order to be included. Standard clinical information was gathered from the hospital records, and we have used the pTNM stages if available; otherwise the cTNM stages were used [10]. Measures of QoL were obtained at the following time points to the best of our ability: at diagnosis, and 6, 9 and 12 months following diagnosis. No new QoL information was collected if the patient's treatment goal was changed to palliative. All patients were observed until death, or to 10-year survival as measured from the time of diagnosis. Fifty-eight deaths were observed with median overall survival at 105 months. Prior to the study permission was obtained from the "Regional Committees for Medical and Health Research Ethics", Western Norway branch. All included patients signed informed consent forms.

HN QoL inventories

HN QoL was determined by patients answering the validated Norwegian edition of the European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire (QLQ) H&N-35 [11]. The QLQ H&N-35 comprises seven multi-item scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality), and six symptom items (teeth problems, opening mouth, dry mouth, sticky saliva, coughing, and feeling ill). The answers were given according to a 4-point Likert format. These indices were transformed so that 100 indicated maximum and 0 least symptoms.

A H&N sum score was computed based on the symptom indices from the first 30 questions of the EORTC QLQ

H&N-35 questionnaire. This sum score had Cronbach's α above 0.76, indicating that these scores were internally consistent.

Comorbidities

Comorbidities were obtained with the validated chart-based Adult Comorbidity Evaluation scale (ACE)-27 measured at baseline [12]. The ACE-27 grades specific conditions into levels of severity: mild, moderate, or severe. Based on the highest ranked single ailment an overall comorbidity score (none, mild, moderate, or severe) was assigned. In cases with two or more moderate ailments registered in different disease entities, the overall comorbidity score was designated as severe.

Smoking and alcohol consumption

The estimated weekly consumption of cigarettes was self-reported at the time of diagnosis, and scored as currently smoking (yes/no). Alcohol consumption was determined by selecting one of the following statements: never, less than 1 time per week, 1–2 times per week, previously more than 2 times per week, and presently more than 2 times per week.

Hr-HPV analysis

Analyses were performed as we have previously published in *Nature* [13]. In short, DNA was extracted from formalin-fixed paraffin-embedded (FFPE) specimens. These were tissues from primary HNSCC tumors in diagnostic or surgical samples or from lymph node metastatic lesions. For detection of HPV DNA standard Gp5 + /Gp6 + primers were used. The PCR reaction mix consisted of Multiplex Mastermix PCR kit (Qiagen GmbH, Hilden, Germany), 2 µl primer mix and 2 µl DNA run in a volume of 20 µL. The samples were inactivated by heating (95 °C) for 15 min and then run 38 cycles at 94 °C for 45 s, 43 °C for 90 s and 72 °C for 90 s and finally 72 °C for 10 min.

The PCR products were separated and visualized on a 3% agarose gel. First, the PCR products were purified by incubation with ExoStar (GE Healthcare, Buckinghamshire, UK) at 37 °C for 15 min followed by enzyme inactivation at 80 °C for 15 min. The purified PCR products were then prepared for sequencing using the same primers as for the initial PCR reaction in combination with BigDye® Terminator v1.1 Cycle Sequencing kit (Life Technologies, Foster City, CA). Before analyzing on a 3130XL Genetic Analyzer (Life Technologies, Foster City, CA) the products of the sequencing reaction was purified using BigDye® Xterminator kit (Life Technologies, Foster City, CA). The HPV DNA sequences were identified using the NCBI BLAST database. Regularly, more than 98% homology was observed with NCBI BLAST.

We have previously studied HPV status of a general cohort of HNSCC patients in Western Norway diagnosed during the time span where the current patients were recruited without determining a single case of an HPV tumor positive patient with primary site outside oropharynx [14]. Therefore, we have only determined HPV status among the oropharyngeal SCC patients. The rest of the patients were designated as HPV negative.

Statistics

Statistical significance was considered if $p < 0.05$ with two-sided tests. Overall survivals were registered from the National Population Register of Norway. The H&N sum score was analyzed either scored continuously or as a dichotomized variable with the highest scoring quartile (most symptoms) compared to the remaining three lower quartiles. The QoL indices were analyzed as continuous variables with Cox regression analyses or dichotomized in Kaplan–Meier analyses. The proportional assumption was assessed graphically. We used a commercially available statistical program package (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 24.0. IBM Corp, Armonk, NY).

Results

Socio-demographic and clinical characteristics of the cohort are presented in Table 1. The mean ± standard deviation (SD) age of the patients was 61 ± 9 years at the time of diagnosis, and 86% of the participants were men. Cancer of the oral cavity was the most common tumor site (31%). Twenty-six per cent of the patients, as evaluated with the ACE-27, presented with moderate or severe levels of comorbidity.

Survival prediction of socio-demographic and clinical variables

Baseline socio-demographic and clinical variables survival predictions were examined in univariate Cox regression analyses (Table 1). Male gender was associated with worse prognosis ($p = 0.042$). A high ACE-27 score predicted subsequent lower survival ($p = 0.01$), as did T-stage ($p = 0.008$). At diagnosis, a history of high alcohol consumption ($p = 0.025$) or current smoking ($p = 0.035$) was significantly predictive of worse survival. Whether subjected or not to primary tumor surgery also predicted prognosis (Table 1).

Survival prediction from the H&N QoL sum score

The prognostic information based on the H&N QoL sum score is presented in Table 2. The H&N QoL sum score was found to predict survival when obtained at the time of diagnosis ($p = 0.006$), at 6 months ($p = 0.02$), at 9 months

Table 1 Patient characteristics including socio-demographics, clinical information, and treatment, as well as univariate prognostic value

Characteristics	No.	HR (95% CI)	*p* value
Age in years (61 ± 9 years)		1.03 (1.00–1.06)	0.047
Gender		2.9 (1.04–7.94)	0.042
Female (reference)	15		
Male	91		
Education[a]		1.06 (0.92–1.21)	0.450
High school or less	66		
College or more	40		
Currently smoking[a]		1.76 (1.04–2.97)	0.035
No	58		
Yes	47		
Alcohol consumption[a]		1.28 (1.03–1.60)	0.025
Never	7		
Less than 1 time per week	45		
1–2 times per week	31		
Previously more than 2 times per week	9		
More than 2 times per week	14		
ACE-27 comorbidity		1.40 (1.08–1.80)	0.010
None	44		
Mild	34		
Moderate	19		
Severe	9		
Tumor site			
Laryngeal	26	0.60 (0.31–1.16)	0.128
Oral cavity	33	1.29 (0.75–2.21)	0.361
Oropharyngeal	27		
Others	20		
Tumor stage		1.35 (1.08–1.69)	0.008
0	7		
1	28		
2	37		
3	19		
4	15		
Nodal stage		1.18 (0.91–1.54)	0.216
0	48		
1	13		
2	42		
3	3		
HPV status		0.57 (0.28–1.16)	0.120
Tumor negative	84		
Tumor positive	22		
Treatment			
Tumor surgery	80	0.84 (0.28–0.84)	0.010
Neck dissection	51	1.53 (0.91–2.56)	0.110
Free flap reconstruction	21	0.86 (0.44–1.65)	0.640
Tumor radiotherapy	87	1.96 (0.89–4.32)	0.096
Neck radiotherapy	78	1.58 (0.84–2.98)	0.159
Chemotherapy	11	1.22 (0.55–2.69)	0.624

[a]Self-reported at diagnosis

($p = 0.002$), and at 12 months ($p = 0.05$); i.e., the more reported symptoms, the worse prognosis. In multivariate Cox regression analyses, the H&N QoL sum score likewise predicted survival even with adjustment for patient variables: at diagnosis ($p = 0.030$), at 6 months ($p = 0.047$), at 9 months ($p = 0.006$), and at 12 months ($p = 0.043$). Further multivariate Cox analyses, including TNM stage as co-variates, showed that QoL scores measured at diagnosis ($p = 0.020$) and at 6 months ($p = 0.037$) still predicted survival. Combining both patient and tumor variables with the QoL sum score did not yield significant QoL survival predictions. Analyses based on the dichotomized H&N QoL sum score showed the same survival predictions when evaluated at the time of diagnosis: $p = 0.08$; at 6 months: $p = 0.018$; and at 9 months: $p < 0.001$ (Fig. 1). When the questionnaire responses were obtained at 9 months, the H&N QoL sum score predicted survival with adjustment for clinical variables, as well as the parallel H&N QoL sum score obtained at diagnosis (HR = 1.03) with confidence interval (CI): 1.01–1.05 ($p = 0.016$). We have also analyzed the survival prediction of the dichotomized H&N QoL 9 months sum score in a multivariate Cox regression analysis including gender, age, TNM stage, ACE scale, self-reported smoking status, alcohol intake as well as whether primary tumor surgery, whether neck dissection was performed, whether radiation therapy was given, whether neck RT was given and whether chemotherapy was utilized. The QoL score still showed a trend towards survival prediction (HR = 2.3; CI 0.91–6.28; $p = 0.077$) (Table 3).

Survival prediction from the H&N QoL indices

The univariate survival predictions of the continuously scored H&N QoL indices are presented in Table 4. The following QoL indices were predictive of survival when obtained at the time of diagnosis: "pain", "swallowing", "social eating", "teeth problems" and "coughing". At 6 months, the demonstrated significant QoL survival predictions were "pain", "swallowing", "social eating", "teeth problems," and "feeling ill". At 9 months, all the same H&N QoL indices were found to predict survival, and in addition the H&N QoL indices of "sexuality" and "sticky saliva". When obtained at 12 months "speech", "coughing", and "feeling ill" predicted survival. The H&N QoL domain "feeling ill" measured at 6, 9 and 12 months still predicted survival when adjusted by the same index measured at the time of diagnosis (results not shown). Cox stepwise regression analyses internally weighing all the H&N-35 QoL indices, were also performed at all measured time points. These analyses showed that the H&N QoL domain "social eating" demonstrated the strongest survival prediction (Table 5).

Table 2 Significant uni- and multivariate Cox regression analyses evaluating 10-year overall survival prediction from the EORTC H&N QoL sum score measured continuously; obtained at the time of diagnosis and at 6, 9, and 12 months following diagnosis

H&N sum score[b]	Univariate			Multivariate including patient characteristics[a]			Multivariate including gender, age of patient, and TNM stage		
	HR	95% CI for HR	*p* value	HR	95% CI for HR	*p* value	HR	95% CI for HR	*p* value
At diagnosis	1.02	1.01–1.04	0.006	1.02	1.00–1.02	0.030	1.03	1.00–1.04	0.020
At 6 months	1.02	1.00–1.03	0.02	1.02	1.00–1.02	0.047			
At 9 months	1.03	1.01–1.04	0.002	1.03	1.01–1.05	0.006	1.02	1.00–1.04	0.037
At 12 months	1.02	1.00–1.04	0.05	1.03	1.00–1.05	0.043			

HR hazard ratio, *CI* confidence interval

[a]Adjusted by age, gender, hr-HPV tumor status, Adult Comorbidity Evaluation scale (ACE)-27, self-reported smoking status and alcohol intake; all co-variates obtained at diagnosis

[b]Sum score of all EORTC QLQ H&N-35 indices (except from questions 31–35)

Survival prediction of the H&N QoL sum score stratified by hr-HPV tumor status

In general, the H&N QoL scores of tumor hr-HPV-positive and hr-HPV-negative patients showed similar predictive results. This is demonstrated by the hr-HPV-stratified Kaplan–Meier analyses of the H&N QoL sum score in Fig. 1, as well as for the H&N QoL index "swallowing" in Fig. 2.

Discussion

In this study, we demonstrate significant prognostic value of HN-specific QoL data on long-term (10 years) survival. The prognostic value was presently demonstrated with EORTC H&N QoL data obtained at the time of diagnosis as well as at 6, 9, and 12 months. These survival predictions were to some extent independent of hr-HPV tumor status, gender, age, health behaviors as well as TNM stage. The specific H&N QoL indices "pain", "swallowing", "social eating", "teeth problems," and "feeling ill" were found to be predictive of survival at minimum 3 out of 4 QoL obtained time points in univariate analyses.

The present findings are in accordance with, and extend our previous results regarding survival predictions of EORTC H&N QoL sum scores [6, 15]. We have previously shown that both a general symptom QoL sum score and the H&N QoL sum score were found to be predictive of survival; both when measured at the time of diagnosis [6, 15], as well as when evaluated among successfully treated patients with more than 18 months follow-up [16, 17]. The results are furthermore in line with a number of other published studies [4, 5, 18–23], showing survival predictions from pre-treatment QoL scores. It is also supported from previous research that post-treatment QoL scores obtained during the first year following diagnosis may predict survival [4, 24].

In this paper, we have additionally employed a H&N QoL sum score derived from the EORTC QLQ H&N-35 questionnaire even though this sum score is not officially recognized by the EORTC. The H&N QoL sum score was found to be predictive of survival at the time of diagnosis as well as throughout the 12 months following diagnosis. Patient-derived QoL scores are remarkably stable over time [25]. On this basis, it is not surprising that the same index from the same patient collected at different time points predicted survival. On the other hand, each measuring point represents a patient answering a QoL questionnaire without any specific help to recall previous answers. This adds to the validity of the QoL questionnaires and to the reliability of the current survival predictions.

All QoL scores are to some extent based on the patient's mental assessment of physical functions. The H&N QoL index "social eating" represents, e.g., evaluation of the eating, which presumably includes the whole act from putting the food into the mouth, via chewing and swallowing, to transporting the food to the stomach. This index predicted survival well. Thus, the source of survival prediction may be of both physical, but also mental origin. To separate these sources of survival prediction is an interesting matter for future research.

The survival rate of HNSCC patients depends amongst other factors on the hr-HPV tumor status [26]. We [15] have previously suggested that the QoL-derived survival predictions, like presently studied, do not depend on the hr-HPV tumor status, even though oropharyngeal SCC hr-HPV-positive patients have an entirely different biology underlying the cancer than hr-HPV-negative counterparts [26]. Therefore, we have stratified by hr-HPV tumor status in the analyses, and observed no changed survival prediction of H&N QoL scores. This argues that QoL-based

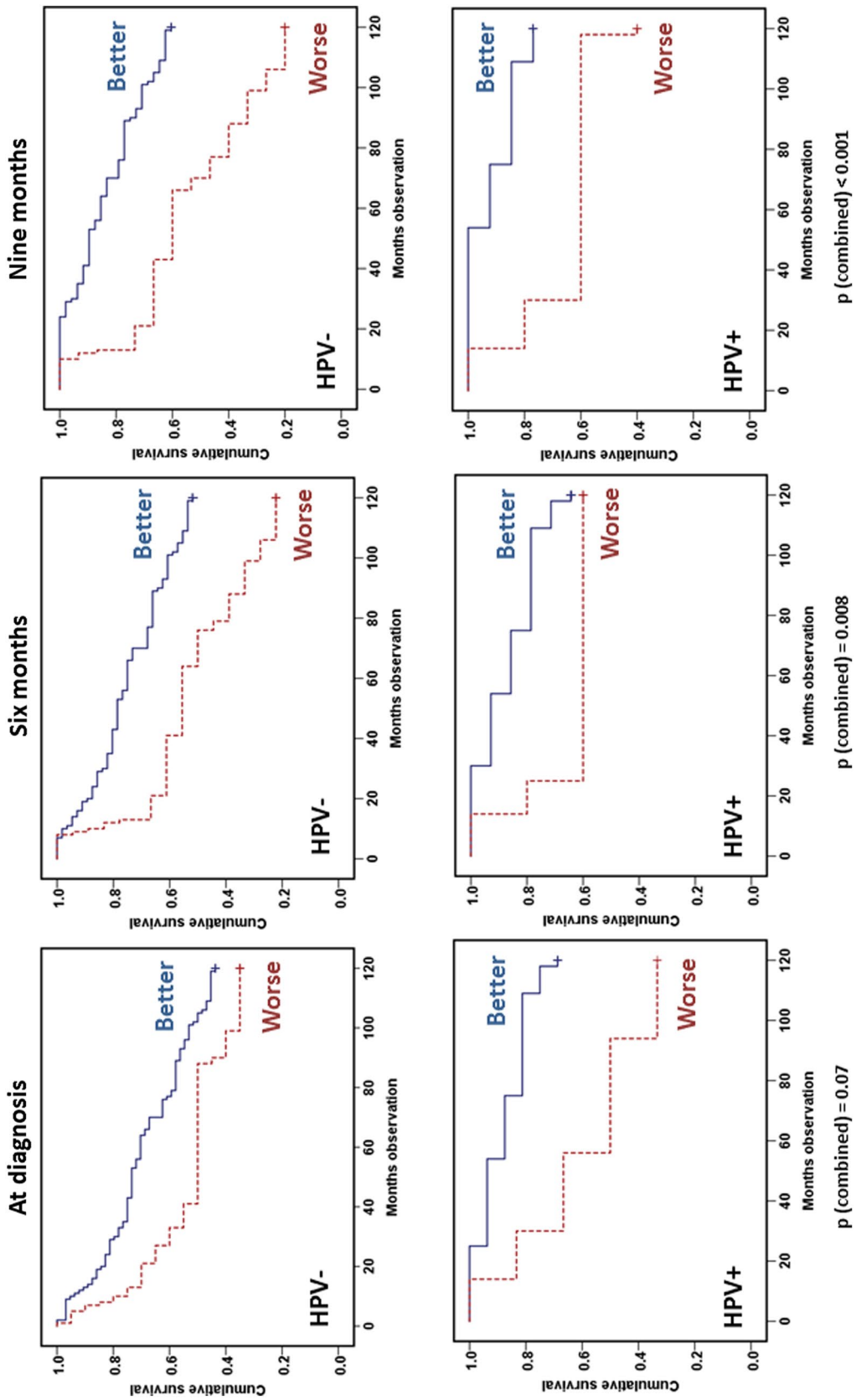

Fig. 1 Kaplan–Meier overall survival curves from EORTC QLQ H&N-35 sum scores of indices obtained at diagnosis (left column), 6 (middle column) and 9 (right column) months, stratified by hr-HPV negative (upper row) and hr-HPV-positive (lower row) infection of the tumors. The sum scores were dichotomized with the worst scoring quartile forming one group and the other patients the second group. High symptom scores are shown by a red, dotted line. Low symptom scores are shown by a blue, continuous line. Statistics by combined log-rank analyses with hr-HPV tumor infection as stratification variable

Table 3 Multivariate Cox regression analyses evaluating 10-year overall survival prediction from the EORTC H&N QoL sum score measured binomially obtained at 9 months following diagnosis with patient, health behavior, TNM stage, and treatment information included as co-variates

Co-variates	*p* value	HR	95,0% CI for HR	
			Lower	Upper
Gender	0.129	3.19	0.71	14.3
Age	0.026	1.06	1.01	1.12
T-stage	0.107	1.32	0.94	1.86
N-stage	0.292	1.36	0.77	2.42
ACE-27	0.424	1.16	0.81	1.65
Alcohol history	0.425	1.16	0.81	1.67
Smoking status	0.270	1.59	0.70	3.60
Primary tumor surgery	0.956	1.02	0.39	2.70
Neck dissection	0.834	1.09	0.50	2.37
Radiation therapy (RT)	0.534	0.57	0.10	3.32
Neck RT	0.893	0.89	0.17	4.79
Chemotherapy	0.902	1.08	0.32	3.66
H&N sum score	0.077	2.39	0.91	6.28

HR hazard ratio, *CI* confidence interval, *ACE-27* Adult Comorbidity Evaluation scale-27

Table 5 Stepwise Cox regression analyses evaluating 10-year overall survival prediction from all the EORTC QLQ H&N-35 indices (30 first questions) obtained at diagnosis; and at 6, 9, and 12 months following diagnosis

EORTC QLQ H&N-35 index	*p* value	HR	95% CI for HR	
			Lower	Upper
At diagnosis				
Swallowing	0.008	1.02	1.01	1.04
Teeth problems	0.015	1.01	1.00	1.02
Coughing	0.016	1.01	1.00	1.02
At 6 months				
Social eating	0.007	1.02	1.00	1.02
At 9 months				
Social eating	0.001	1.02	1.01	1.03
At 12 months				
Social eating	0.037	1.01	1.00	1.03
Coughing	0.007	1.01	1.01	1.04

HR hazard ratio, *CI* confidence interval

survival predictions may be similar in other cancer diseases, as also suggested by other investigators [27].

The validated chart-based Adult Comorbidity Evaluation scale (ACE)-27 [12] has previously been shown to predict both survival [18] and be associated with QoL scores [28] among HNSCC patients. The ACE-27 score predicted survival in this study. Despite this, when included as a co-variate in multivariate analysis, we did not find removal of the significant survival prediction from the H&N QoL sum score. However, it is still possible that a more detailed knowledge of the health condition of the patients could have explained more of the determined survival prediction.

Disease extent at diagnosis governs which treatment each patient is given, predicts prognosis, and affects QoL scores in HNSCC patients [29]. Extensively treated patients may have a worse prognosis and lowered QoL simply due to this relation. Therefore, the prognostic power from QoL scores

Table 4 Significant and trend results according to univariate Cox regression analyses evaluating 10-year overall survival prediction from the EORTC QLQ H&N-35 indices measured continuously; obtained at the time of diagnosis and at 6, 9, and 12 months following diagnosis

EORTC QLQ-H&N-35 index	At diagnosis		At 6 months		At 9 months		At 12 months	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Pain	1.01 (1.00–1.02)	0.026	1.01 (1.00–1.03)	0.031	1.02 (1.00–1.03)	0.015		
Swallowing	1.02 (1.01–1.04)	0.001	1.01 (1.00–1.02)	0.010	1.02 (1.01–1.03)	0.003		
Senses								
Speech							1.02 (1.00–1.03)	0.048
Social eating	1.01 (1.00–1.02)	0.023	1.01 (1.00–1.02)	0.009	1.01 (1.00–1.03)	0.005	1.01 (1.00–1.02)	0.072
Social contact					1.01 (1.00–1.03)	0.053		
Sexuality	1.01 (1.00–1.02)	0.060			1.01 (1.00–1.02)	0.007		
Teeth problems	1.01 (1.01–1.02)	0.001	1.01 (1.00–1.02)	0.033	1.01 (1.00–1.02)	0.007		
Opening mouth								
Dry mouth								
Sticky saliva			1.01 (1.00–1.02)	0.096	1.01 (1.00–1.02)	0.035		
Coughing	1.01 (1.00–1.02)	0.003					1.02 (1.01–1.04)	0.002
Feeling ill			1.02 (1.00–1.03)	0.006	1.02 (1.01–1.03)	0.008	1.02 (1.00–1.04)	0.015

HR hazard ratio, *CI* confidence interval

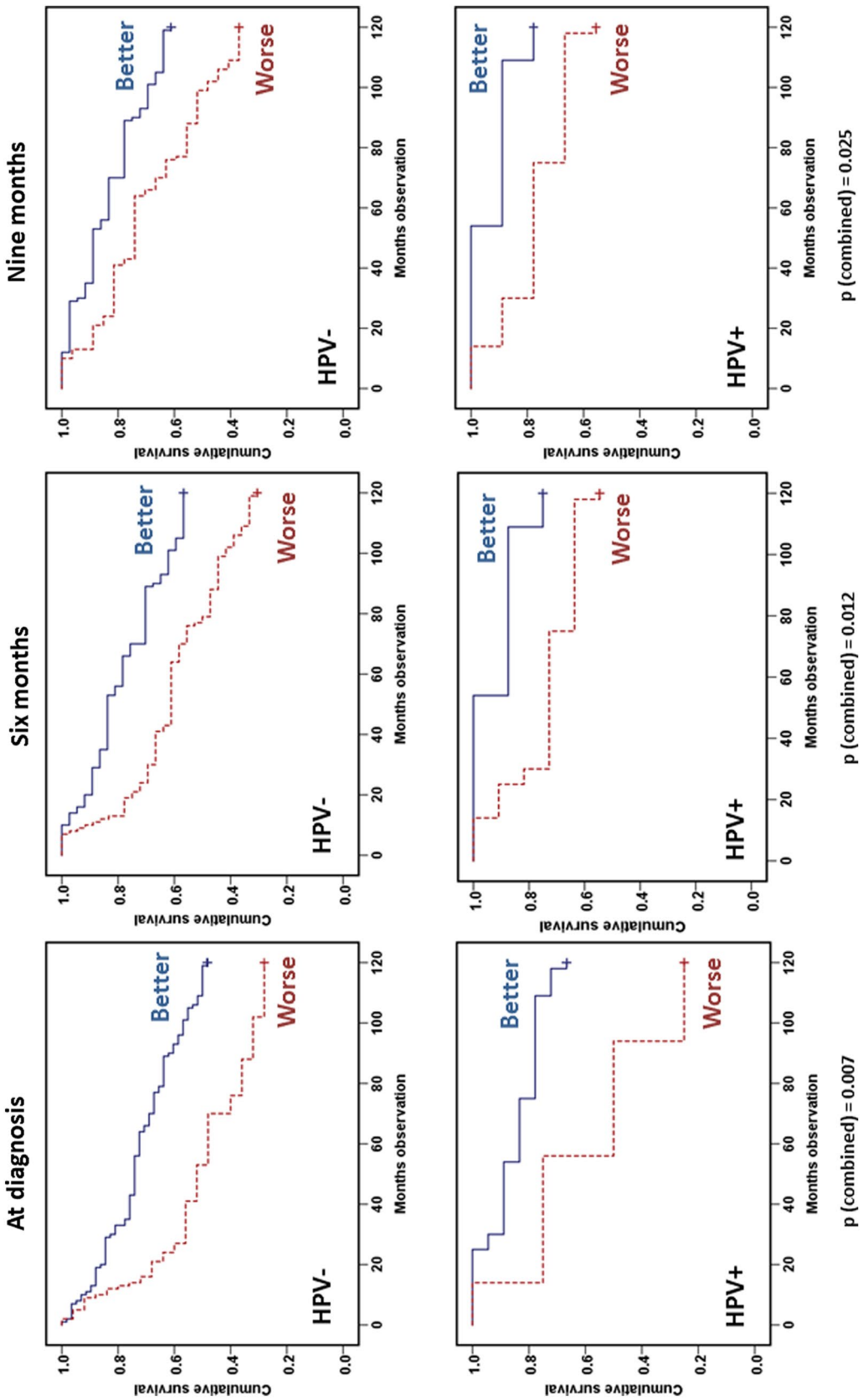

Fig. 2 Kaplan–Meier overall survival curves from the EORTC QLQ H&N-35 swallowing index obtained at diagnosis (left column), 6 (middle column) and 9 (right column) months, stratified by hr-HPV negative (upper row) and hr-HPV-positive (lower row) infection of the tumors. The sum scores were dichotomized by median value with high symptom score (red, dotted line) versus low symptom score (blue, continuous line). Statistics by combined log-rank analyses with HPV tumor infection as stratification variable

obtained following treatment should be studied adjusted for TNM stage. We have done so, and demonstrated that QoL scores obtained at diagnosis and at 6 months following diagnosis when adjusted for TNM stage still predicted survival. Including information of comorbidity, smoking, alcohol history in addition to treatment information, we have furthermore determined a trend towards survival prediction with QoL sum scores from data obtained 9 months following diagnosis. The trend only may be due to the limited number of patients included with lower statistical power when adding many co-variates; or in fact showing the mechanism behind the observed prognostic power of QoL scores when obtained following treatment.

Several authors have studied if reported high levels of pain by patients contain information about impaired survival. The published results so far do not allow firm conclusions, but it is possibly the case among cancer patients [30]. The present results support this claim.

We [15] and others [4, 24] have previously shown that QoL scores obtained following treatment predicted survival, adjusted by the corresponding scores at diagnosis. This is also to some extent the case concerning the present data.

We further suggest that the QoL monitoring may have clinical relevance. Presently, we have, e.g., shown a substantially elevated overall mortality among the quartile of patients reporting the highest symptom burden. Thus, health care professionals providing treatment and surveillance to HNSCC patients may find prognostic information that can be utilized when choosing which patients should have the closest follow-up both aimed at the index HNSCC disease and any present comorbidity.

It is of interest to note that the scored rate of "swallowing" predicted survival well. A hypothesis to explain this is that swallowing difficulties are associated to aspiration, which in turn causes aspiration pneumonia with subsequent mortality. Based on this and corresponding knowledge, interventions in relation to, e.g., nutrition [31] and swallowing [32] status seem warranted among former HNSCC patients, and should be a focus for future studies.

Limitations

There are certain limitations to this study. With a limited number of patients included, especially with disease originating from many sites, this imposes difficulties when evaluating the results in a site-specific manner. Furthermore, the primary endpoint in this study was overall mortality. Cause of death could provide additional information. In the future, larger survival prediction studies concerning QoL and with cause of death included should be performed.

Conclusions

In conclusion, we have shown that HN QoL scores obtained at diagnosis and at several time points during the first year following diagnosis predicted subsequent survival. The survival prediction was independent of hr-HPV tumor status, and to some extent independent of TNM stage, level of comorbidities, and health behaviors. The present findings seem to have important clinical applications, and QoL survival predictions like the ones presently presented, should be studied in more detail.

Funding This work has been supported by the Norwegian Cancer Society.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by the authors. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and its subsequent amendments and was approved by the institutional review board according to national regulations.

Informed consent A written, informed consent was obtained from all participants of the study.

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