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ORIGINAL REPORT

Health-Related Quality of Life As a Survival Predictor for Patients With Localized Head and Neck Cancer Treated With Radiation Therapy

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ABSTRACT

Purpose
To assess the added prognostic value for overall survival (OS) of baseline health-related quality of life (HRQOL) and of early changes in HRQOL among patients with localized head and neck cancer (HNC) treated with radiation therapy.

Patients and Methods
All 540 patients with HNC who participated in a randomized trial completed two HRQOL instruments before radiation therapy: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the Head and Neck Radiotherapy Questionnaire. Six months after the end of radiation therapy, 497 trial participants again completed the two HRQOL instruments. During the follow-up, 179 deaths were observed. Multivariate Cox proportional hazards models were used to test whether HRQOL variables, baseline and change, provided additional prognostic value beyond recognized prognostic factors.

Results
The baseline EORTC QLQ-C30 physical functioning (PF) score was an independent predictor of OS. The hazard ratio (HR) associated with a 10-point increment in baseline PF was 0.87 (95% CI, 0.81 to 0.94). In multivariate models, the change in HRQOL was significantly associated with OS for most HRQOL dimensions. Among these, PF change was the strongest predictor. The magnitude of the association between PF change and survival decreased over time. At 1 year, the HR associated with a positive PF change of 10 points was 0.75 (95% CI, 0.68 to 0.83). After PF is taken into account, no other HRQOL variable was associated with survival.

Conclusion
Our findings indicate that both baseline PF and PF change provide added prognostic value for OS beyond established predictors in patients with HNC. Assessing HRQOL could help better predict survival of cancer patients.

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INTRODUCTION

Health-related quality of life (HRQOL) has become a standard end point in randomized controlled trials in oncology and may contribute to clinical decision making by presenting important information from the patient perspective.[1] Patient self-assessment of HRQOL could provide prognostic survival information beyond what is achieved by recognized factors.[2-4] Measurements of HRQOL at the time of initial therapy have often been shown to be independent predictors of overall survival (OS) for patients with advanced cancer[2-5] but not for those with early-stage cancer.[6-8] The prognostic significance of changes in HRQOL scores after the initial course of treatment has also been examined with mixed results.[2,7,9-11]

Head and neck cancer (HNC) is associated with significant morbidities. Adverse effects of radiation therapy and surgery further affect HRQOL of patients with HNC. A few studies have examined the relationship between pretreatment HRQOL and survival among patients with HNC.[12-17] In multivariate analyses, physical self-efficacy,[12] physical component summary,[17] cognitive functioning,[13] social functioning,[13] and fatigue[14] were associated with OS. Two studies assessed whether changes in HRQOL after diagnosis and treatment were related to survival.[14,18] In one study, change in the physical component of the Medical Outcomes Study Short

Form Health Survey (SF-36) during the first year following diagnosis was a significant predictor of disease-specific survival.[18]

We prospectively collected HRQOL data on 540 patients with stage I or II HNC treated by radiation therapy as part of a randomized trial assessing the effects of a supplementation with α-tocopherol and β-carotene.[19-21] In this study, we assessed whether pretreatment HRQOL parameters and changes in HRQOL from baseline until 6 months after the end of radiation therapy significantly improved outcome prediction for OS beyond what was accomplished by recognized prognostic factors.

PATIENTS AND METHODS

Study Population

Between October 1, 1994, and June 6, 2000, 540 patients with stage I or II HNC were recruited in five radiation therapy centers in the province of Québec, Canada. The institutional review board of each participating center approved the study protocol. All patients gave written informed consent before being randomly assigned. Patients were randomly assigned to receive a daily supplementation consisting of one capsule of vitamin E (400 IU *dl*-α-tocopherol) and one capsule of β-carotene (30 mg) or placebos during radiation therapy and for 3 years after radiation therapy ended. The trial was continued with α-tocopherol alone. The supplementation had adverse effects on second primary cancers and OS.[19-21]

HRQOL

HRQOL was assessed by the Quality of Life Questionnaire C30 (QLQ-C30) a general instrument developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC).[22] This instrument is a 30-item questionnaire that incorporates five functional scales and global health status (scored zero to 100, with 100 for perfect functioning) and several symptom scores (scored zero to 100, with zero for no symptoms). As an example, physical functioning (PF) is evaluated by a scale based on the following five yes/no items[22]: (1) Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? (2) Do you have any trouble taking a *long* walk? (3) Do you have any trouble taking a *short* walk outside of the house? (4) Do you have to stay in a bed or a chair for most of the day? (5) Do you need help with eating, dressing, washing yourself or using the toilet?" This scale ranges from zero to 100 with six possible discrete values (zero, 20, 40, 60, 80, or 100) for a given patient. In addition, HRQOL was evaluated by a validated HNC-specific quality-of-life instrument (Head and Neck Radiotherapy Questionnaire [HNRQ]).[23] This 22-item instrument incorporates six domain-specific scores and a global score using a 1 to 7 scale, with 7 for no symptoms. These two HRQOL instruments were completed by the participants at baseline; at the end of radiation therapy; and at follow-up visits 1, 6, 12, 24, and 36 months after the end of radiation therapy.

Follow-Up

Follow-up information was obtained by the collaborating radiation oncologists and the study nurses every 6 months during the 3 years after the end of radiation therapy, and then once a year until the end of the study. Records were linked with the Québec mortality files by using the unique Québec health insurance identifier from enrollment until December 31, 2004, for all but 10 participants who did not consent to this record linkage. All death certificates were obtained from the Institut de la statistique du Québec.

Statistical Analyses

Two separate analyses were performed. First, the relationship between baseline HRQOL and OS was assessed for all 540 participants with follow-up time starting at the time they were randomly assigned. Second, the relationship between changes in HRQOL and OS was assessed for the 497 participants with HRQOL data at baseline and at 6 months after the end of radiation therapy. The change in HRQOL was defined as the value at the visit 6 months after the end of radiation therapy minus the baseline value. In this latter analysis, follow-up time was counted from the visit 6 months after the end of radiation therapy. For both analyses, follow-up continued until the date of last visit (for the 10 participants mentioned previously), the date of death, or December 31, 2004.

The relationship between baseline HRQOL or HRQOL changes and mortality was assessed by using Cox proportional hazards models.[24] In the analysis of baseline HRQOL, univariate Cox models were used to select the HRQOL variables associated with mortality that had P values $< .05$. The hazard ratios (HRs) were calculated for increments of 10 points for EORTC QLQ-C30 variables and for increments of 1 point for HNRQ variables because such changes are considered clinically meaningful.[23,25,26] The HRQOL variables were kept as continuous variables because this scale was judged appropriate based on the martingale residuals. A reference multivariate Cox model was developed that included all known predictors of mortality that remained statistically significant ($P < .05$) after adjustment for all the other variables in the model. Each baseline HRQOL variable selected in the univariate model step was then added in turn to the reference multivariate model to form an extended model. In accordance with the objective, the significance of the contribution of each HRQOL variable was judged by the partial likelihood ratio test comparing the extended model with the reference model.[24,27] The HRQOL variables that were associated with $P < .05$ were considered for further analysis. The lack of multicollinearity between these HRQOL variables was verified.[28] The HRQOL variable associated with the smallest P value was added to the reference model, and the process was repeated until no additional HRQOL variable improved prediction. The proportionality assumption and the overall goodness of fit of the extended models were verified. To provide a reference for HRQOL variables, a similar analysis was conducted for Karnofsky performance status (KPS).[29]

In the analysis of the changes in HRQOL between baseline and the visit 6 months after the end of radiation therapy, the same strategy was followed. Cox models that included both the baseline variable (to control confounding by baseline value) and the change variable were used to select the HRQOL change variables associated with mortality with $P < .05$. The same predictors of mortality as those for baseline data were included in the reference multivariate

Table 1. Baseline Personal and Clinical Characteristics of Trial Participants (N = 540)

Characteristic	No.	%
Age, years		
Mean	62.5	
SD	9.8	
Sex, male	425	79
Education, primary school only	232	43
Married	399	74
No. of drinks per day during previous 10 years		
Mean	1.8	
SD	3.5	
Smoking during previous year	343	64
Family income < $30,000 per year	337	62
Body mass index, kg/m^2		
Mean	26.1	
SD	4.7	
Stage II head and neck cancer	208	39
Laryngeal cancer	450	83
Randomly assigned to supplement arm of trial	273	51
Karnofsky performance status		
Mean	96.5	
SD	7.4	
Charlson comorbidity index		
Mean	0.61	
SD	0.96	

Abbreviation: SD, standard deviation.

Table 2. HRs and 95% CIs for Death Determined on the Basis of Personal and Clinical Data Obtained in the Reference Multivariate Cox Model

Variable	Adjusted HR	95% CI
Cancer stage, II *v* I	1.79	1.30 to 2.46
Cancer site, larynx *v* others	0.55	0.38 to 0.78
Age, 1-year increment	1.07	1.05 to 1.09
Smoking in previous year, yes *v* no	1.57	1.12 to 2.19
Alcohol intake during previous 10 years, one drink per day increment	1.04	1.01 to 1.08
Body mass index, ≤ 20 *v* > 20 kg/m^2	1.94	1.19 to 3.18
Trial arm assignment, supplement *v* placebo	1.37	1.02 to 1.86

NOTE. Each HR is adjusted simultaneously for all the other variables in the table.
Abbreviation: HR, hazard ratio.

Cox model. Each HRQOL change variable selected in the initial step was then added, together with its baseline counterpart, in turn to the reference multivariate model. Because the proportionality assumption was not met for some of the HRQOL change variables in the extended models, an interaction term between change in HRQOL and the log of follow-up time was added, when necessary, to improve the adequacy of the extended models. In accordance with the objective, the statistical significance of the contribution of each HRQOL change variable was judged by the partial likelihood ratio test, which compared the extended model with the model that included the recognized predictors plus the baseline HRQOL variable.[24,27] The HRQOL change variables associated with $P < .05$ were considered for further analysis. As for the baseline data, the process was repeated until no additional HRQOL change variable improved prediction. As a reference, KPS change was also examined.

To assess the robustness of the findings concerning the baseline and change HRQOL variables ultimately selected by the approaches described above, we also conducted general stepwise Cox regression multivariate models that included all established clinical and personal predictors plus KPS and all HRQOL variables. The associations between HRQOL variables and mortality are presented as HRs with their 95% CIs. All statistical tests are two sided. The analyses were conducted with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

The baseline personal and clinical characteristics of the study participants are listed in Table 1. After a median follow-up of 6.5 years, 179 deaths were observed among the 540 participants. The independent predictors of overall mortality in the study population are listed in Table 2 with their HRs and associated 95% CIs. The baseline scores for all dimensions of the two HRQOL instruments are listed in Table 3. Because the patients in the trial had localized HNC, the baseline functioning scores of the EORTC QLQ-C30 were relatively high, and the symptom scores were usually moderate. The same pattern was observed for HRQOL variables from the HNRQ. In univariate survival analyses, the following variables were associated with mortality ($P < .05$): PF, role functioning, dyspnea, and constipation from the EORTC QLQ-C30 and mouth score from the HNRQ. Of these five HRQOL variables, three (PF, role functioning, and dyspnea) significantly improved outcome prediction (see extended models in Table

Table 3. Baseline HRQOL Measures and Associated HRs for Death

Variable	HRQOL Score		Univariate Model		Extended Multivariate Model		
	Mean	SD	HR	*P*	HR	95% CI	*P**
EORTC QLQ-C30							
Physical functioning	88.5	18.0	0.85	< .0001	0.87	0.81 to 0.94	.00063
Role functioning	90.0	23.6	0.94	.04	0.93	0.89 to 0.99	.019
Emotional functioning	76.8	23.2	1.03	.32			
Cognitive functioning	87.7	18.3	1.05	.22			
Social functioning	91.6	17.6	0.99	.89			
Fatigue	17.1	21.0	1.02	.67			
Nausea and vomiting	3.0	9.3	0.94	.47			
Pain	11.9	19.6	1.04	.23			
Dyspnea	21.0	24.9	1.07	.01	1.06	1.00 to 1.12	.045
Sleep disturbance	25.2	32.7	1.04	.10			
Appetite loss	7.6	18.6	1.01	.78			
Constipation	11.6	23.8	1.07	.03	1.03	0.97 to 1.09	.42
Diarrhea	4.7	13.9	1.00	.92			
Financial impact	12.9	25.4	0.96	.22			
Global health status	72.4	21.8	0.98	.46			
HNRQ							
Mouth	6.47	0.75	0.79	.004	0.92	0.77 to 1.10	.35
Skin	6.93	0.32	0.75	.21			
Throat	5.82	1.06	0.98	.79			
Digestion	6.74	0.53	1.27	.13			
Energy	6.02	1.26	0.90	.06			
Psychosocial	5.82	1.17	1.05	.43			
Global	6.32	0.58	0.85	.18			

NOTE. HRs associated with HRQOL measures correspond to a 10-point increment for EORTC QLQ-C30 scores and to a 1-point increment for HNRQ scores. The extended multivariate models included all variables in Table 2 plus, for each model, the baseline HRQOL value.
Abbreviations: HRQOL, health-related quality of life; HR, hazard ratio; SD, standard deviation; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; HNRQ, Head and Neck Radiotherapy Questionnaire.
**P* value determined on the basis of the partial likelihood ratio test.

3). After taking PF into account, neither role functioning nor dyspnea were any longer associated with mortality. The HR associated with a 10-point increment (on a scale of zero to 100) in PF was 0.87 (95% CI, 0.81 to 0.94). Baseline KPS was an independent predictor of mortality after adjusting for the seven recognized prognostic factors. The HR for a 10-point increment in KPS score (on a scale of zero to 100) was 0.76 (95% CI, 0.64 to 0.90). However, after PF was taken into account, KPS was no longer associated with mortality (HR, 0.84; 95% CI, 0.70 to 1.02).

The relationship between changes in HRQOL and overall mortality was assessed among the 497 participants with HRQOL data both at baseline and 6 months after the end of radiation therapy. After a median follow-up of 5.8 years, 147 deaths were observed. The changes are presented in Table 4. On average they were moderate. The changes of greatest magnitude were observed for an improvement in emotional functioning, for a reduction of sleep disturbance on the EORTC QLQ-C30, and for an increase in mouth symptoms on the HNRQ. In Cox models containing both baseline and change values for a given HRQOL dimension, several change variables were associated ($P < .05$) with mortality (Table 4). Each HRQOL change variable selected in the initial step was then added, together with its baseline counterpart, in turn to the reference multivariate model. A total of 13 HRQOL change variables were associated with mortality with P values $< .05$. For three HRQOL change variables (PF, role functioning, and fatigue) the magnitude of the association with mortality decreased with follow-up time ($P < .05$ for interaction). For these three variables, an interaction term between HRQOL change and the log of follow-up time was added to improve the adequacy of the models. Change in PF was the HRQOL change variable with the smallest P value. After PF was controlled for, no other HRQOL change variable significantly improved outcome prediction. The effect of change in PF on mortality was more pronounced early in the follow-up and decreased regularly throughout the follow-up period. The HR at 1 year was 0.75 for a positive change of 10 points (95% CI, 0.68 to 0.83). The partial likelihood ratio test indicated that the two variables—change in PF and interaction of the change variable with follow-up time—significantly improved the predictive capacity of the multivariate Cox model containing the seven known predictors plus baseline PF (likelihood ratio test: $P = 4.6 \times 10^{-6}$). Six months after the end of radiation therapy, the change in PF was a stronger predictor for OS (adjusted χ^2 statistic, 43.27; 2 *df*; $P = 4.0 \times 10^{-10}$) than the baseline PF score (adjusted χ^2 statistic, 24.82; 1 *df*; $P = 6.3 \times 10^{-7}$). KPS change (mean, −0.97; standard deviation, 7.61) was not associated with mortality in multivariate Cox models (HR associated with a 10-point increase in Karnofsky score, 0.85; 95% CI, 0.69 to 1.05).

Table 4. Changes in HRQOL Measures and Associated HRs for Death

	HRQOL Change		Bivariate Model		Extended Multivariate Model		
Variable	Mean	SD	HR	*P*	HR	95% CI	*P**
EORTC QLQ-C30							
Physical functioning	+0.04	16.8	0.86	.0007	0.75†	0.68 to 0.83	4.6×10^{-6}
Role functioning	−1.41	29.2	0.91	.002	0.85‡	0.79 to 0.91	.00011
Emotional functioning	+5.85	23.1	0.92	.03	0.91	0.84 to 0.99	.024
Cognitive functioning	−0.60	20.9	0.92	.03	0.91	0.84 to 0.99	.037
Social functioning	+0.70	21.6	0.91	.02	0.89	0.82 to 0.97	.011
Fatigue	+2.12	22.8	1.09	.02	1.17§	1.06 to 1.28	.0097
Nausea and vomiting	−0.60	11.6	0.69	.51			
Pain	+0.27	22.8	1.05	.17			
Dyspnea	+0.67	26.3	1.04	.19			
Sleep disturbance	−4.02	33.0	1.03	.40			
Appetite loss	+2.75	24.8	1.12	.0001	1.06	0.99 to 1.13	.064
Constipation	−0.07	24.3	1.12	.002	1.09	1.02 to 1.16	.021
Diarrhea	−0.34	19.7	1.07	.13			
Financial impact	−3.15	26.9	1.03	.41			
Global health status	+1.79	22.6	0.91	.01	0.91	0.84 to 0.99	.023
HNRQ							
Mouth	−0.61	1.07	0.81	.001	0.83	0.71 to 0.97	.022
Skin	−0.10	0.59	0.70	.001	0.81	0.65 to 1.01	.096
Throat	+0.04	1.26	0.85	.02	0.79	0.69 to 0.91	.0016
Digestion	−0.05	0.73	0.69	.002	0.74	0.58 to 0.94	.020
Energy	−0.06	1.45	0.91	.12			
Psychosocial	+0.004	1.43	0.84	.004	0.83	0.73 to 0.94	.0045
Global	−0.17	0.72	0.68	.002	0.67	0.53 to 0.83	.00047

NOTE. HRs associated with changes in HRQOL measures correspond to a 10-point increment for EORTC QLQ-C30 scores and to a 1-point increment for HNRQ scores. The extended multivariate models included all variables in Table 2 plus, for each model, the change in HRQOL together with its baseline value and, when required ($P < .05$), an interaction term between the change and the log of time.

Abbreviations: HRQOL, health-related quality of life; HR, hazard ratio; SD, standard deviation; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; HNRQ, Head and Neck Radiotherapy Questionnaire; exp, exponent.

*P value determined on the basis of the partial likelihood ratio test.

†HR and CI at 1 year in the follow-up; more generally, formula for HR is: HR = exp (−0.29 + 0.13 log of time).

‡HR and CI at 1 year in the follow-up; more generally, formula for HR is: HR = exp (−0.17 + 0.07 log of time).

§HR and CI at 1 year in the follow-up; more generally, formula for HR is: HR = exp (0.15 − 0.07 log of time).

It is worth noting that the stepwise approach gave results similar to those described above, and also identified PF and PF change as the sole HRQOL variables that could improve outcome prediction. For illustrative purposes, Kaplan-Meier curves are presented to describe the crude relationships of baseline PF (Fig 1) and change in PF with OS (Fig 2).

DISCUSSION

There are two main findings in this study conducted among patients with HNC with stage I or II disease treated with radiation therapy. First, patients' reported PF score before therapy provides prognostic information for OS beyond what is accomplished by data on the seven recognized factors. Second, changes in PF from baseline until 6 months after the end of radiation therapy further improve the prognostic information for OS beyond these seven prognostic factors and pretreatment PF. The effect of change in PF decreases over time. KPS score, a physician assessment of the level of patient activity and medical requirements, is widely used in oncology and has been shown to be associated with patient survival.[29] Our study confirms previous evidence that patients' self-reported HRQOL data outperform KPS in the prediction of OS.[14,30,31]

Previous studies have shown that pretreatment HRQOL parameters are prognostic factors in advanced[2-5] or recurrent cancers.[7] A few studies have examined the relationship between pretreatment HRQOL and survival among patients with advanced-stages of HNC.[14-17] In a study of 102 patients with stage III or IV HNC treated by radiation therapy, the EORTC QLQ-C30 fatigue score was the only baseline HRQOL variable significantly associated with OS.[14] In a large cohort of patients with locally advanced HNC, the overall score on the Functional Assessment of Cancer Therapy–Head and Neck was associated with locoregional control in a multivariate Cox model.[16] No HRQOL variable was predictive of OS in this population.[15,16] In a prospective study of 133 patients with HNC, most of them with localized stages, patients' perceived physical abilities and confidence were assessed by the Physical Self-Efficacy Scale.[12] Physical self-efficacy was associated with OS in multivariate models. In another study of patients with HNC, a majority of whom had stage I or II disease, the cognitive functioning score of the EORTC QLQ-C30 was the only HRQOL variable associated with OS in multivariate models.[13] Grignon et al[17] observed 571 patients treated for HNC and used the SF-36 to assess self-reported health at diagnosis and during the first year after diagnosis. The baseline physical component summary of the SF-36 was associated with OS and disease-specific survival after adjusting for cancer stage, site, and comorbidities.

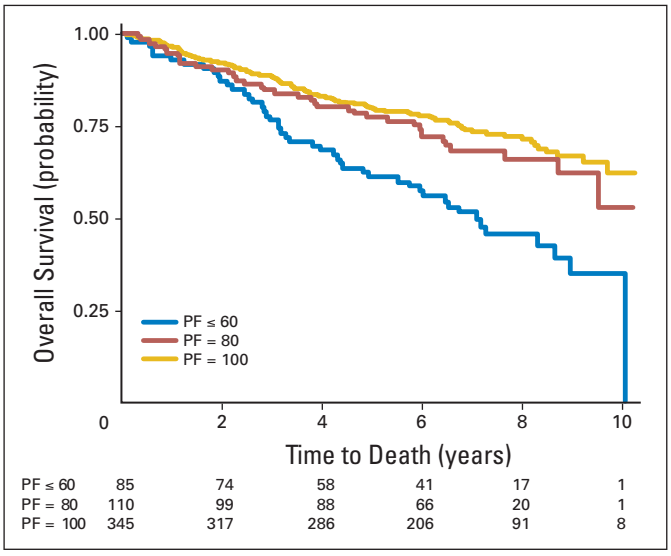

Fig 1. Overall survival according to baseline European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 physical functioning (PF) score (100, 80, or 60, or lower) among 540 patients with head and neck cancer treated with radiation therapy.

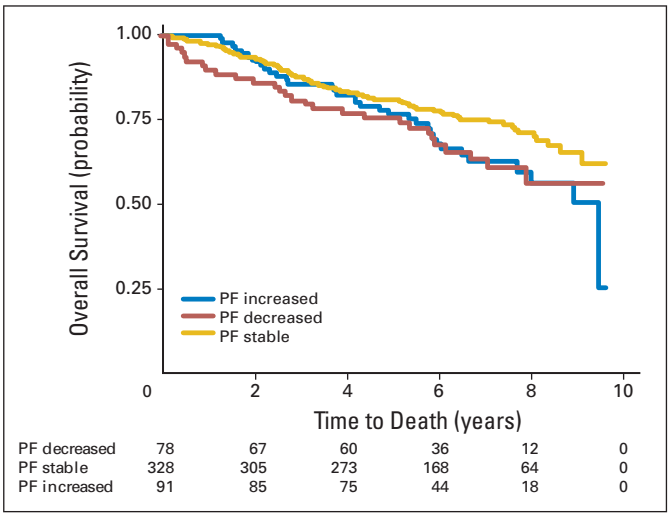

Fig 2. Overall survival according to change in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 physical functioning (PF) score from baseline until 6 months after the end of radiation therapy (PF was stable, PF increased if PF at 6 months was greater than at baseline, or PF decreased if PF at 6 months was lower than at baseline) among 497 patients with head and neck cancer treated with radiation therapy.

A few investigators[20,32-34] have assessed the longitudinal changes of HRQOL in patients with HNC. The general picture is a deterioration of HRQOL during the first 3 months after the start of treatment, followed by a slow recovery. The problems of swallowing, dry mouth, and sticky saliva are more persistent. Abendstein et al[34] assessed the HRQOL of 218 patients with HNC 1 year after the initial treatment using the EORTC QLQ-C30. Those who survived another 5 years had better measures of most HRQOL items than those who died during the 5-year follow-up. The largest difference between survivors and nonsurvivors was for PF. Fang et al[14] measured HRQOL at baseline and during radiation therapy using the EORTC QLQ-C30 and an HNC-specific module among 102 patients with advanced HNC who had been treated with radiation therapy. None of the changes in HRQOL were significantly predictive of survival. In our study, the changes were measured over a longer, perhaps more relevant period. Jameson et al[18] examined the changes in the physical component score of the SF-36 between the time of diagnosis and the 1-year follow-up among 403 patients with HNC. In multivariate models adjusting for cancer site and stage, the changes during the first year were significantly associated with disease-specific survival but not with OS. In our study, many dimensions of HRQOL in addition to PF were associated with mortality, but the associations were no longer present after

change in PF was taken into account. The HNRQ was developed for patients with locally advanced HNC, and it focuses primarily on symptoms.[23] This could explain why, in our study population of patients with stage I or II HNC, HNRQ variables did not improve outcome prediction after both traditional prognostic factors and PF were taken into account. Similarly, the symptom score variables in the EORTC QLQ-C30 were no longer associated with OS once PF was taken into account. De Boer et al[12] observed 133 patients with HNC, most with stage I or II disease. In their study, patients with high perceived physical abilities had a significantly better OS. Head and neck–specific complaints were not associated with survival.

In our large prospective study of patients with localized HNC, both baseline PF and change in PF significantly improved OS prediction beyond traditional prognostic factors. Assessing patients' own perception of HRQOL through simple validated instruments could help better predict long-term outcome and thus contribute to improving quality cancer care. In randomized controlled trials, HRQOL data obtained before randomization could be used as stratifying variables, as is customary with classical prognostic factors. In clinical practice, it would be desirable to systematically collect HRQOL data from patients at the time of diagnosis and again in the few months after the end of the initial therapy. This could be achieved in the context of patient navigation that is now part of many cancer care programs.[35] The HRQOL data obtained by nurse navigators would be useful in planning decisions and tailoring cancer care management to individual patients, guided by prognostic factors based on clinical information as well as on patient self-reported HRQOL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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