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The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy

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SUMMARY

To examine the impact of late treatment-related xerostomia and dysphagia on health-related quality of life (HRQOL) in head and neck cancer (HNC) patients after radiotherapy. A multi-center cross-sectional survey was performed. Patients with a follow-up of at least 6 months after curative radiotherapy, without evidence of recurrent disease were eligible for inclusion. The Euroqol-5D questionnaire (EQ-5D) was filled out and toxicity was scored and converted to the RTOG scale. The EQ-5D measures generic HRQOL in terms of utility and visual analogue scale (VAS) scores. Missing data on the EQ-5D were imputed using multiple imputation. HRQOL was compared between subgroups of patients with and without toxicity. Subsequently, the impact of xerostomia and dysphagia on HRQOL was analyzed using multivariate regression analyses. Both analyses were performed separately for utility scores and VAS scores. The study population was composed of 396 HNC patients. The average utility and VAS scores were 0.85 (scale 0–1) and 75 (scale 0–100). Subgroups of patients with xerostomia and/or dysphagia showed statistically significantly lower utility and VAS scores ($P = 0.000–0.022$). The multivariate regression model showed that xerostomia and dysphagia were negative predictors of both utility and VAS scores. Other factors which influenced HRQOL in at least one of the two regression models were: sex, tumor location and the addition of surgery to radiotherapy. Xerostomia and dysphagia diminish generic HRQOL. Moreover dysphagia affects patients' HRQOL stronger than xerostomia.

Introduction

An increasing number of options become available for the treatment of head and neck cancer (HNC). Traditionally, treatment decisions were primarily based on local tumor control and the length of survival. However, treating HNC often involves a trade-off between (disease-free) survival and treatment-related toxicity. After radiotherapy, in particular xerostomia and dysphagia negatively affect health-related quality of life (HRQOL).[1,2] Therefore, the length of survival after treatment has to be weighed against the quality of survival. As a result, HRQOL and factors influencing HRQOL (such as treatment-related toxicity) are increasingly recognized as important treatment outcomes in HNC.[1,3–5]

To take into account HRQOL, disease-specific measures are often used. Although these questionnaires are relevant for patients and physicians, the main disadvantage of disease-specific measures is their inability to compare HRQOL in different disease areas. In contrast, generic HRQOL can be compared in different disease areas. Measures of generic HRQOL assess the preferences of individuals for a certain health status; the more preferable the outcome, the higher the score.[6] This can be measured by inquiring how patients value their own health status (patients' perspective) or based on the preferences of the society (general public perspective). Preferences for health states can be combined with life

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expectancy, resulting in quality adjusted life years (QALYs). The main advantage of QALYs is that they capture life expectancy and quality of life in a single measure.[6] This is useful to inform the aforementioned trade-off between length of survival and treatment-related toxicity (quality of survival).

Previous studies have assessed health state preferences in HNC.[7–11] However, to our knowledge, no study provided health state preferences based on subgroups distinguished by treatment-related toxicity for primary treated HNC patients. Hence, knowledge on the impact of toxicity on generic HRQOL is lacking. Therefore, we aimed to examine the impact of late treatment-related xerostomia and dysphagia on HRQOL (patient and general public perspective) in disease free HNC patients treated with radiotherapy.

The aim of this study was twofold: (1) to compare HRQOL across subgroups subdivided by xerostomia and dysphagia and (2) to examine the influence of late treatment-related toxicity on HRQOL.

Materials and methods

Conceptual model

To examine the influence of late treatment-related toxicity on HRQOL, we constructed a conceptual model (Fig. 1). In order to minimize multicollinearity in our analyses, we only included factors that are directly related to HRQOL, excluding indirect factors (i.e. variables that influence HRQOL through other variables).

HRQOL is negatively affected by radiotherapy induced xerostomia and dysphagia.[1,2,12] Since dysphagia may be the consequence of xerostomia, these outcome measures might correlate or even interact. Next to these main variables of interest, other potentially predictive factors were subdivided into patient related factors, disease related factors and treatment-related factors. Patient related factors include sex and age; HRQOL scores are likely to decrease with increasing age and tend to be lower for females.[13–15] Disease related factors include tumor location and disease stage. Tumor location has a varying impact on HRQOL.[1,2,16,17] In contrast, disease stage is unlikely to directly affect HRQOL.[1,2,16,17] In case of a lower HRQOL for patients with advanced disease stage, the decreased HRQOL is suggested to be related to cancer treatment, treatment toxicity and/or disease progression rather than to cancer stage directly[2,16,18] Hence, disease stage can be considered as an indirect predictor of HRQOL and is for this reason not included in our conceptual model. Finally, with regard to treatment-related factors, the combination of radiotherapy with surgery or chemotherapy is suggested to have a negative influence on HRQOL.[1,16] The interval after radiotherapy (follow-up period) has a varying impact on HRQOL.[1,19]

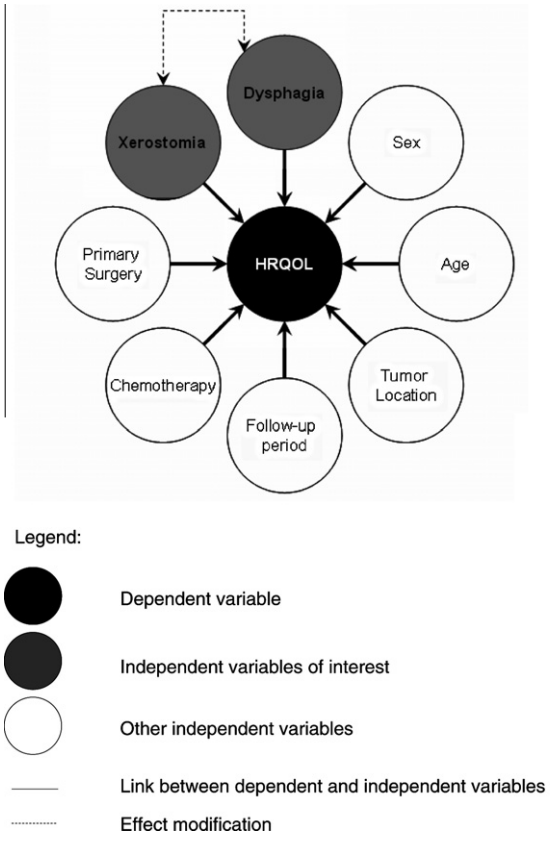

Figure 1 Conceptual model.

Data collection

From June 2009 to March 2010, a multi-center cross-sectional survey was performed during planned follow-up visits in two Dutch hospitals.[20] The study population consisted of HNC patients, who were treated with curative intend by radiotherapy alone or combined with surgery and/or chemotherapy. Patients with a follow-up period of 6 months or longer after the start of radiotherapy and without evidence of recurrent disease were eligible for inclusion.

The EuroQol-5D questionnaire[21] (EQ-5D) was filled out in the hospital before the patients visited their physician. During the follow-up visit, severity of xerostomia and dysphagia was scored by a trained researcher (radiation technologist) or the treating physician and converted to the RTOG scale[22] (Appendix 1). The following data were retrieved from patients' medical records: date and type of initial treatment, primary tumor location and initial tumor stage. This study was approved by the Institutional Review Board.

EuroQol-5D

The EQ-5D is the most frequently used multi-attribute health status classification system and is recommended by the National Institute for Health and Clinical Excellence.[6,21,23–25] The EQ-5D consists of questions considering five dimensions of generic HRQOL (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[21] The answers to these questions can be combined to calculate health state preferences (so-called utility scores) from a general public perspective using a scoring function. This scoring function was based on the preferences of 2.997 UK respondents, who valued 42 different health states from the EQ-5D using the time trade-off method (TTO).[26] Utility scores calculated by this scoring function range from −0.59 (health state worse than death, severe problems in all five dimensions), through 0 (death) to 1 (full health, no problems in all dimensions). Next to the five questions, a visual analogue scale (VAS) is included in the EQ-5D that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).[21] The VAS measures the patients' self-rated HRQOL (patients' perspective).[27]

Data analyses

Missing data

Patients with missing data for late toxicity scores were excluded from the analyses. As recommended for handling missing HRQOL data,[28] missing data on the EQ-5D were replaced using multiple imputation. To impute the missing values on the five questions and the VAS score of the EQ-5D, five datasets were created ($m = 5$). The imputation model included the variables

described in the conceptual model (Fig. 1), plus the questions and VAS of the EQ-5D. Categorical variables were imputed as scale variables and variables containing more than two categories were converted into dummy variables.[29,30] After multiple imputation, values for the separate questions of the EQ-5D were converted back to categorical variables.[29]

To obtain pooled estimates of the mean, variance and parametric tests the method as described by Rubin[31] and more recently by Carlin et al.[32] was used. There is no generally accepted method for pooling the (adjusted) R^2, medians, quartiles and non-parametric tests. The (adjusted) R^2 was pooled by averaging the separate values for the (adjusted) R^2 from all five regression analyses. Medians and quartiles were pooled by obtaining the median and quartiles of all five imputed datasets combined. Non-parametric tests were pooled by averaging the test statistic for the separate tests for all five imputed datasets, which was subsequently used to calculate *p*-values.

Analyses

First, descriptive statistics were computed for the population characteristics.

Second, we examined differences in utility and VAS scores between subgroups with toxicity and without toxicity. For this purpose, patients were subdivided according to grade 0, 1, 2 and $\geqslant 3$ for both xerostomia and dysphagia. Only subgroups with $\geqslant 10$ patients were included in the analyses. Subsequently, skewness and kurtosis of the HRQOL distribution within these subgroups were examined. If the skewness and kurtosis fell between −2.0 and 2.0, the differences between subgroups were compared using one way analysis of variance (ANOVA) and if significant multiple paired Student's *t*-tests were performed. Kruskal–Wallis tests and if statistically significant pairwise comparison Mann–Whitney *U* tests were performed if the skewness or kurtosis exceeded this range.

Third, to test the conceptual model presented in Fig. 1, utility and VAS scores were separately included as dependent variables in multivariate regression analyses. The variables which were considered to influence HRQOL were included in the regression model as independent variables. Grade of xerostomia and dysphagia, as well as sex, tumor location, surgery of the primary tumor and chemotherapy were included as categorical variables. Xerostomia and dysphagia were subdivided into dummy variables for grade 0 (reference category), 1, 2 and $\geqslant 3$. For tumor location dummy variables were created for oral cavity and lip, pharynx, larynx and other sites (reference category). Larynx and pharynx were separate categories since laryngeal carcinomas are typically early stage tumors and subsequently treated with limited radiation fields as opposed to pharynx carcinomas which are mostly locally advanced and treated with large radiation fields. Further, age and follow-up period after radiotherapy were included as scale variables. Since there is a possible interaction between xerostomia and dysphagia, effect modification (by means of an interaction term) was considered between these two variables.

Independently of the significance, none of the potentially influencing variables were excluded from the regression model. Only the interaction term between xerostomia and dysphagia was excluded if not statistically significant. The final regression models were checked for assumptions of linear regression.

All analyses were performed using SPSS 17.0. *P*-values <0.05 were considered statistically significant.

Results

Population characteristics

Altogether, 92% of all approached patients agreed to participate. In total 426 patients filled out the questionnaire, 30 of these patients were excluded since toxicity data were missing. This resulted in a study population of 396 patients of which 55 patients (14%) had missing values on the EQ-5D which were imputed. Population characteristics are presented in Table 1. The average utility and VAS scores among all 396 patients were 0.85 (sd: 0.18) and 75 (sd: 15), respectively.

HRQOL among patients subdivided by xerostomia and dysphagia

Subgroups were categorized by grades of xerostomia and/or dysphagia (based on the RTOG scale). In total, 84 patients (21%) had no xerostomia or dysphagia. Xerostomia was more prevalent than dysphagia (Table 2).

For the utility scores, a ceiling effect (the scores are clustered around the upper end of the scale) was observed for the subgroup without toxicity. This resulted in a distribution with a high skewness (−2.4) and kurtosis (7.2). For VAS scores, the skewness and kurtosis were within the proposed range. Therefore, subgroup

Table 1
Characteristics of the study population.[a]

Patient characteristics		
Sex		
Male	276	70%
Female	120	30%
Age (years)		
Mean (Sd)	63.2	(11.8)
Minimum, maximum	20	99
Follow-up period (months)		
Median (IR)	20	(23.0)
Minimum, maximum	6	152
Disease characteristics		
Tumor location		
Oral cavity and lip	51	13%
Pharynx	115	29%
Larynx	125	32%
Nasal cavity and sinuses	20	5%
Salivary gland	23	6%
Other[b]	49	12%
Unknown	13	3%
Tumor classification		
Tis	8	2%
T0	17	4%
T1	92	23%
T2	115	29%
T3	55	14%
T4	82	21%
Unknown	27	7%
Node classification		
N0	194	49%
N1	57	14%
N2	121	31%
N3	9	2%
Unknown	15	4%
Stage (UICC)		
0	7	2%
I	55	14%
II	59	15%
III	78	20%
IV	139	35%
Unknown	58	15%
Treatment characteristics		
Surgery of the primary tumor		
No	258	65%
Yes	138	35%
Chemotherapy		
No	339	86%
Yes	57	14%

Abbreviation: Sd, standard deviation; RT, radiotherapy; IR, interquartile range.
[a] Values are numbers/percentages unless stated otherwise.
[b] Including skin and unknown primary tumors.

Table 2
Health-related quality of life categorized by xerostomia and dysphagia.

Utility scores[c]																				
	Xerostomia																			
	0						1						2				3+			
Dysphagia	Mean	(Sd)	Median	(IR)	N	(N imp)	Mean	(Sd)	Median	(IR)	N	(N imp)	Mean	(Sd)	Median	(IR)	N	(N imp)	Mean	(Sd)	Median	(IR)	N	(N imp)
0	0.909	(0.161)	1.000	(0.186)	84	(1)	0.898	(0.138)	1.000	(0.204)	92	(5)	0.846	(0.177)	0.850	(0.275)	15	(2)						0[b]
1	0.841	(0.144)	0.796[a]	(0.275)	18	(3)	0.829	(0.175)	0.814[a]	(0.275)	68	(4)	0.817	(0.187)	0.812[a]	(0.309)	31	(3)						0[b]
2					9[b]		0.803	(0.136)	0.796[a]	(0.133)	14	(6)	0.763	(0.213)	0.778[a]	(0.311)	40	(3)						0[b]
3+					1[b]						6[b]		0.758	(0.234)	0.796[a]	(0.363)	16	(1)						2[b]
Visual Analogue Scale scores[c]																								
0	80.1	(12.4)	80.0	(20.0)	84	(1)	79.5	(14.7)	80.0	(20.0)	92	(5)	76.1	(8.9)	75.0	(10.0)	15	(2)						0[b]
1	73.4	(14.4)	79.0	(10.0)	18	(3)	73.9[c]	(16.0)	75.0	(16.5)	68	(4)	69.9[c]	(14.6)	70.0	(20.0)	31	(3)						0[b]
2					9[b]		73.8	(22.8)	71.6	(16.0)	14	(6)	67.5[c]	(17.1)	70.0	(20.0)	40	(3)						0[b]
3+					1[b]						6[b]		64.8[c]	(13.9)	65.0	(10.0)	16	(1)						2[b]

Abbreviations: Sd, standard deviation; IR, interquartile range; N imp, the number of imputed cases.
[a] Statistically significantly ($P < 0.05$) different utility score than patients without xerostomia and dysphagia (Mann–Whitney *U* test).
[b] Not tested for difference between subgroups ($N < 10$).
[c] Statistically significantly ($P < 0.05$) different visual analogue scale score than patients without xerostomia and dysphagia (Student's *t*-test).

analyses were performed using non-parametric tests for utility scores and using parametric tests for VAS scores.

Utility scores were significantly different between subgroups (Kruskal–Wallis test, $P < 0.001$). Pairwise comparisons showed significantly higher utility scores for patients without toxicity compared to patients with ⩾grade 1 dysphagia independently of the grade of xerostomia. For patients with dysphagia grade 0, average utility scores ranged between 0.91 (xerostomia grade 0) and 0.85 (xerostomia grade 2). For dysphagia grade 1 this ranged between 0.84 and 0.82 and between 0.80 and 0.76 for ⩾grade 2 dysphagia (Table 2 and Fig. 2).

Also VAS scores were significantly different among subgroups (ANOVA, $P < 0.001$). Pairwise comparisons showed significantly lower VAS scores if patients had ⩾grade 1 for both xerostomia and dysphagia, except for the subgroup with grade 1 xerostomia and grade 2 dysphagia. For patients with dysphagia grade 0, average VAS scores ranged between 80 (xerostomia grade 0) and 76 (xerostomia grade 2). For dysphagia grade 1 this ranged between 74 and 70 and between 74 and 65 for ⩾grade 2 dysphagia (Table 2 and Fig. 2).

Factors influencing HRQOL

Utility scores were significantly negatively affected by grade 2 and ⩾3 xerostomia in the multivariate regression analyses (Table 3). This was also true for dysphagia grade 1 and grade 2. Grade 1 xerostomia and ⩾grade 3 dysphagia had no significant impact on utility

Figure 2 HRQOL categorized by grade of xerostomia and dysphagia*. Only subgroups with more than 10 patients are presented, error bars indicate the 95% confidence interval of the mean and values in the bars represent the *N* per subgroup.

Table 3
Multivariate regression model.[a]

Final model (dependent variable = utility score) R^2 = 42%,[b] Adjusted R^2 = 17%[c]			
Independent variables	Beta	Se	*P*-value
Constant	0.836	0.057	0.000
Treatment toxicity			
Xerostomia[d]			
Grade 1	−0.013	0.021	0.540
Grade 2	−0.059	0.028	0.040
Grade 3+	−0.336	0.123	0.006
Dysphagia[d]			
Grade 1	−0.059	0.021	0.005
Grade 2	−0.126	0.029	0.000
Grade 3+	−0.074	0.040	0.060
Patient characteristics			
Sex			
Male	0.052	0.019	0.006
Age	0.000	0.001	0.747
Disease characteristics			
Tumor location[d]			
Oral cavity and lip	0.081	0.030	0.006
Pharynx	0.063	0.027	0.018
Larynx	0.032	0.026	0.226
Treatment characteristics			
Surgery of the primary tumor			
Yes	0.062	0.022	0.006
Chemotherapy			
Yes	0.040	0.027	0.148
Follow-up period	0.000	0.000	0.499
Interaction			
Xerostomia and Dysphagia	–	–	ns
R^2 = 39%[b], Adjusted R^2 = 16%[c]			
Constant	79.4	4.9	0.000
Treatment toxicity			
Xerostomia[d]			
Grade 1	−1.6	1.9	0.412
Grade 2	−7.7	2.6	0.003
Grade 3+	8.2	11.1	0.460
Dysphagia[d]			
Grade 1	−5.6	1.8	0.002
Grade 2	−7.2	3.0	0.026
Grade 3+	−10.8	3.4	0.002
Patient characteristics			
Sex			
Male	1.4	1.7	0.397
Age	−0.1	0.1	0.310
Disease characteristics			
Tumor location[d]			
Oral cavity and lip	5.9	2.7	0.031
Pharynx	4.7	2.3	0.040
Larynx	1.9	2.2	0.398
Treatment characteristics			
Surgery of the primary tumor			
Yes	4.0	2.0	0.043
Chemotherapy			
Yes	4.4	2.4	0.068
Follow-up period	0.0	0.0	0.757
Interaction			
Xerostomia and Dysphagia	–	–	ns

Abbreviations: Se, standard error; ns, not statistically significant.
[a] For the complete case analyses see Appendix.
[b] R^2 = the fraction of the total squared error that is explained by the regression model.[38]
[c] Adjusted R^2 = measure indicating how much variance in the outcome would be accounted for if the model had been derived from the population from which the sample was taken.[38]
[d] Reference category for dummy variables was Grade 0 toxicity and other tumor locations.

scores. Other significant influencing variables were sex, tumor location and whether surgery of the primary tumor was performed. The interaction term for xerostomia and dysphagia was not significant and therefore excluded from the regression model.

VAS scores were significantly negatively influenced by grade 2 xerostomia in the multivariate regression analyses (Table 3). Also, all grades of dysphagia (grade 1, 2 and $\geqslant$3) had a significantly negative impact on VAS scores. Xerostomia grade 1 and $\geqslant$3 had no significant impact on VAS scores. Other statistically significant variables in the regression model were: tumor location, whether surgery of the primary tumor was performed and whether patients received chemotherapy. The interaction term for xerostomia and dysphagia was not statistically significant and therefore excluded from the regression model.

The regression models were checked for the assumptions of linear regression and no severe deficiencies were observed.

Discussion

To the best of our knowledge, this study was the first to analyze the impact of late treatment-related toxicity on patient-rated utility and VAS scores in HNC. Our analyses demonstrated that dysphagia and xerostomia both have a negative impact on HRQOL. Moreover, dysphagia had the largest impact on HRQOL. Except for age, follow-up period and whether patients received chemotherapy all independent variables reported in the conceptual model (Fig. 1) were significant predictors of HRQOL in at least one of the two regression analyses. The relations were as expected, except for surgery. The complete case analyses resulted in comparable regression models (Appendix 2).

Potential limitations of this study included the low number of patients with grade $\geqslant$3 toxicity (Table 2). This might explain the fact that grade $\geqslant$3 dysphagia was not a significant predictor of utility scores. The same may apply to grade $\geqslant$3 xerostomia for VAS scores. Also, the cross-sectional design and hence the inability to correct for baseline HRQOL may be considered as a limitation. However, we corrected for potentially confounding variables and to our knowledge there was no rationale to assume that the HRQOL before treatment was on average different between the subgroups subdivided by treatment toxicity. Therefore, the impact of late treatment-related toxicity on HRQOL in our study can probably not be attributed to the cross-sectional design. Nevertheless, prospective studies measuring utility and VAS scores in HNC patients with different grades of toxicity are needed to confirm our results. Finally, we included patients who had a follow-up period of at least 6 months from treatment start. This includes patients who have been studied 4–5 months following completion of radiotherapy. It is unclear whether xerostomia and dysphagia have stabilized after this period. However, additional analyses showed that if the 21 patients (5%) with a shorter follow-up than 6 months from treatment completion were excluded, the HRQOL estimates stratified by xerostomia and dysphagia remained similar.

The current study showed on average relatively higher utility than VAS scores. In contrast with our results, previous studies indicated that patients with a specific condition (patients' perspective) are inclined to place higher scores for their own health state compared with non-patients (general public perspective), presumably due to adaptation.[33–36] However, corresponding with our results, most studies indicated that due to differences in measurement methods, utility scores based on the TTO method (as in this study) are higher than VAS scores.[6,33] Despite these abovementioned differences between utility and VAS scores, the decrements between the subgroups subdivided by xerostomia and dysphagia were comparable between the two methods. Therefore, the differences between utility and VAS scores probably represent an overall shift in HRQOL for all subgroups and do not alter the estimated impact of xerostomia and dysphagia on HRQOL.

Previously, utility scores in HNC have been estimated using various methods.[7–11] Based on the EQ-5D filled out by 50 oncology nurses, Brown et al. reported an average utility score of 0.86 for post-treatment HNC patients with loco-regional disease control.[7] This corresponds with the overall average utility score of 0.85 in our study. Ringash et al. applied the TTO method in 112 disease free laryngeal cancer patients resulting in a higher utility score of 0.91.[10] Due to difference in patient populations or subgroups it was not possible to compare utility scores from the other studies with our results.[8,9,11]

Marra et al.,[37] defined 0.03 as a minimally important difference in utility scores (measured by the EQ-5D). Accordingly, the main clinical implications of our results are that treatment strategies aimed at reducing dysphagia and/or xerostomia have the potential to result in a meaningful improvement of generic HRQOL. This emphasizes that next to the expected length of survival also treatment toxicity should be considered when treatment choices are made. Our results can be used to inform this trade-off. In consideration of this trade-off, xerostomia is more prevalent than dysphagia, whereas dysphagia has a higher impact on HRQOL than xerostomia. Therefore, preventing xerostomia could benefit more patients, whereas preventing dysphagia might have a larger benefit per patient.

To reduce treatment toxicity, it may be useful to focus on patients who have the highest risk of experiencing xerostomia and/or dysphagia. In our study population, 84 patients (21%) had no toxicity. Compared with the 312 patients (79%) with any grade of toxicity, the patient group without toxicity consisted of less patients with advanced disease stage (III/IV: 27% versus 62%), had relatively less pharyngeal cancer patients (29% versus 43%) and more laryngeal cancer patients (36% versus 5%). Hence, patients with advanced disease stage and/or pharyngeal cancer may have a higher chance of experiencing xerostomia and/or dysphagia. However, this needs to be confirmed in prospective studies.

In conclusion, our results can be used to support clinical decision making. They underscore the importance that, next to survival data, clinical studies examine toxicity and its impact on generic HRQOL. This assists the trade-off between length and quality of survival. Our study suggests that xerostomia and dysphagia have a negative impact on HRQOL; moreover it was found that dysphagia affects patients' HRQOL stronger than xerostomia.

Conflict of interest statement

No actual or potential conflicts of interest exist.

Ethic statement

The work has been approved by the appropriate ethical committees related to the institutions in which it was performed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.oraloncology.2011.05.012.

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