VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Late Treatment-Related Toxicity on Quality of Life Among Patients With Head and Neck Cancer Treated With Radiotherapy

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Submitted October 10, 2007; accepted April 24, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2622-3770/$20.00

DOI: 10.1200/JCO.2007.14.6647

A B S T R A C T

Purpose
To investigate the impact of treatment-related toxicity on health-related quality of life (HRQoL) among patients with head and neck squamous cell carcinoma treated with radiotherapy either alone or in combination with chemotherapy or surgery.

Patients and Methods
The study sample was composed of 425 disease-free patients. Toxicity was scored according to the European Organisation for Research and Treatment of Cancer (EORTC)/Radiation Therapy Oncology Group (RTOG) late radiation-induced morbidity scoring system. HRQoL was assessed using the EORTC Quality of Life Questionnaire C30. These assessments took place at 6, 12, 18, and 24 months after completion of radiotherapy. The analysis was performed using a multivariate analysis of variance.

Results
Of the six RTOG scales investigated, two significantly affected self-reported HRQoL, salivary gland ($RTOG_{xerostomia}$) and esophagus/pharynx ($RTOG_{swallowing}$). Although $RTOG_{xerostomia}$ was reported most frequently, HRQoL was most affected by $RTOG_{swallowing}$, particularly in the first 18 months after completion of radiotherapy.

Conclusion
Late radiation-induced toxicity, particularly $RTOG_{swallowing}$ and $RTOG_{xerostomia}$, has a significant impact on the more general dimensions of HRQoL. These findings suggest that the development of new radiation-induced delivery techniques should not only focus on reduction of the dose to the salivary glands, but also on anatomic structures that are involved in swallowing.

J Clin Oncol 26:3770-3776. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Treatment of patients with head and neck squamous cell carcinoma may involve radiotherapy, surgery, and/or chemotherapy. Although more patients are being cured of their disease, a substantial percentage of survivors suffer from significant treatment-related adverse effects. Head and neck cancer and its treatment can affect both disease-specific health-related quality of life (HRQoL; eg, salivary and swallowing functions) and the more general domains of HRQoL, such as physical, mental, and social health.

Traditionally, a distinction has been made between early and late adverse effects. In general, adverse effects that occur during or immediately after completion of radiotherapy and subsequently decrease with time are classified as early. In contrast, late adverse effects are generally considered irreversible and progressive and, therefore, are probably more relevant to cancer survivors' HRQoL. In many clinical studies, late radiation-induced toxicity is graded using one of the available grading systems that rate the severity of a range of adverse effects.[1-4] The latter toxicity grading system not only takes into account adverse effects induced by radiotherapy, but also those induced by other treatment modalities such as surgery and chemotherapy.

Although many studies have investigated the HRQoL of patients with head and neck cancer, only a few have focused on the impact of treatment-related adverse effects on HRQoL. Jensen et al[5] investigated the correlation between physician-rated Danish Head and Neck Cancer Group toxicity ratings and HRQoL and found that all Danish Head and Neck Cancer Group toxicity ratings significantly correlated with one or more general HRQoL domains of the European Organisation for Research

and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). However, in this study, the association between treatment toxicity and HRQoL was investigated only at the univariate level. Given that various toxicities may themselves be correlated, a more appropriate approach would be to examine the association between toxicity and HRQoL in a multivariate context.

The purpose of the current prospective study was to evaluate the association between radiation-induced morbidity and HRQoL among patients treated for head and neck squamous cell carcinoma with radiotherapy alone or in combination with surgery and/or chemotherapy. The hypothesis to be tested was that radiation-induced toxicity as assessed by the Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring System is associated significantly with patients' self-reported HRQoL.

PATIENTS AND METHODS

Patients

Beginning in 1997, a prospective cohort of patients with head and neck cancer referred for radiotherapy was established at the Department of Radiation Oncology of the VU University Medical Center (Amsterdam, the Netherlands). In total, this prospective cohort includes 458 patients who were alive and disease free 6 months after completion of radiotherapy. To be included in the current analysis, patients had to have squamous cell carcinoma of the mucosal surfaces of the oral cavity (excluding the lip), oropharynx, nasopharynx, hypopharynx, or larynx and had to be treated with curative radiotherapy between 1997 and 2003, either alone or in combination with chemotherapy or surgery. Patients had to be free of local recurrence or distant metastases at the time of HRQoL assessment.

Treatment

Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). In all patients, planning computed tomography scan was used, and all patients were treated with three-dimensional conformal radiotherapy without attempts to spare the salivary glands. Patients included in this analysis were treated with radiotherapy alone, radiotherapy with chemotherapy, or surgery followed by postoperative radiotherapy (Table 1). Primary radiotherapy was generally delivered with an accelerated fractionation schedule, 2 Gy per fraction, six times per week to a total dose of 70 Gy.

Chemoradiotherapy generally consisted of cisplatin 100 mg/m^2 on days 1, 22, and 43 concomitantly with conventionally fractionated radiotherapy, 2 Gy per fraction, five times per week, to a total dose of 70 Gy. Postoperative radiotherapy was administered with a conventional fractionation schedule to a total dose of 56 to 66 Gy depending on the presence of risk factors, such as surgical resection margin and lymph node metastases with extranodal spread.

Assessment of RTOG Late Radiation-Induced Morbidity

In 1997, a Standard Follow-Up Program was started in the Department of Radiation Oncology for all patients with head and neck cancer treated with primary and/or postoperative (chemo)radiation. Acute and late radiation-induced adverse effects were assessed according to the RTOG/EORTC Late Radiation Morbidity Scoring System. Baseline and follow-up morbidity were assessed by the physician on a weekly basis during radiation for 8 consecutive weeks and at regular intervals thereafter. For the purpose of this study, only the data on late radiation-induced adverse effects were used, including late reactions of the skin ($RTOG_{skin}$), subcutaneous tissue ($RTOG_{subcutanuous}$), mucous membrane ($RTOG_{mucosal}$), larynx ($RTOG_{larynx}$), salivary gland ($RTOG_{xerostomia}$), and esophagus ($RTOG_{swallowing}$).

HRQoL Assessment

For the evaluation of HRQoL, the EORTC QLQ-C30 (version 3.0) was used.[6] The patients completed the baseline questionnaire approximately 1 week before the start of radiotherapy, and follow-up questionnaires were completed at 6 weeks and 6, 12, 18, and 24 months after completion of radiotherapy. The assessments of HRQoL and late radiation-induced morbidity took place on the same day during regular clinic (follow-up) visits, before the visits to the physician. The physicians were blinded to the outcome of the questionnaires at the time of toxicity scoring. For purposes of the current analysis, which is focused on the association between late treatment-induced morbidity and HRQoL, only assessments made at 6 months or later were used.

Table 1. Patients Characteristics

Characteristic	No. of Patients	%
Sex		
Female	112	26
Male	313	74
Age, years		
≤ 65	267	63
> 65	158	37
Treatment modalities		
Radiotherapy alone	216	51
Chemoradiation	61	14
Postoperative radiotherapy	148	35
Tumor classification		
T1	110	26
T2	143	34
T3	92	22
T4	80	19
Node classification		
N0	262	62
N1	37	9
N2a	11	3
N2b	74	17
N2c	30	7
N3	11	3
UICC stage		
I	84	20
II	114	27
III	55	13
IV	172	41
Site		
Larynx	186	44
Oropharynx	125	29
Oral cavity	84	20
Hypopharynx	25	6
Nasopharynx	5	1

Abbreviation: UICC, International Union Against Cancer.

Statistics

Following standard EORTC scoring procedures, all scales of the EORTC QLQ-C30 were linearly converted to a 0 to 100 scale. To analyze the association between the clinical prognostic factors and HRQoL, general linear model (GLM) multivariate analysis of variance (MANOVA) was used. The GLM-MANOVA approach can be used to test the hypothesis of a significant association between a set of interrelated dependent variables (in this study, the HRQoL scales) and one or more grouping variables. This method was preferred over analysis of each HRQoL scale separately because it also takes into account the correlation among the individual HRQoL scales. This multivariate approach also protects against type I errors. In the present study, the GLM-MANOVA was performed in two steps. First, to investigate the association of a given prognostic factor with HRQoL, a univariate analysis was performed to establish whether the prognostic factor was associated significantly with any of the HRQoL measures. Wilks' λ (often referred to as the U-statistic) was used to test the impact of each prognostic variable included in the multivariate model on HRQoL. In addition, the factors that were significantly associated with HRQoL in this first step of the analysis

were entered into the multivariate model. In case of a significant association between a prognostic factor and all HRQoL scales taken together, a second analysis was performed to investigate the association between that factor and each HRQoL scale separately.

In the GLM-MANOVA, in addition to the RTOG late morbidity scales, a number of other potential confounding factors were entered into the model, including sex (male *v* female), age (18 to 65 *v* > 65 years), tumor stage (stage I *v* II *v* III *v* IV), treatment modality (radiotherapy alone *v* chemoradiotherapy *v* surgery and postoperative radiotherapy), and primary tumor site (oral cavity *v* oropharynx/nasopharynx *v* hypopharynx/larynx), one by one and were identified as confounder if the regression coefficient changed by more than 10%. This initial analysis was performed using the assessments made at 6 months after completion of radiotherapy.

In the current study, the mean scores of the HRQoL scales observed among patients with a grade 1, 2, or 3 to 4 toxicity were compared with the scores observed among patients with a grade 0. The clinical relevance of the differences in the mean scores of the HRQoL scales between groups was classified by calculating the effect size using Cohen's D coefficient. An effect size of ≥ 0.20 to 0.49 is generally considered small, ≥ 0.50 to 0.79 is considered moderate, and ≥ 0.8 is considered large.[7,8] Finally, to investigate whether the impact of the RTOG late morbidity scales changed over time, the effect sizes at the other time points (ie, 12, 18, and 24 months after completion of radiotherapy) were calculated as well.

RESULTS

Sample Description

The majority of patients (72.7%) were male. The median age was 61 years (range, 24 to 88 years). Tumor and node classification were assigned according to the staging system of the International Union Against Cancer. The patients' pretreatment characteristics are listed in Table 1.

Compliance

Of the 458 patients at risk at 6 months after completion of radiotherapy, 425 (93%) returned the questionnaire. The compliance was 94% at 12 months (331 of 352 patients alive), 96% at 18 months (252 of 263 patients alive), and 93% at 24 months (191 of 205 patients alive).

Association Between Prognostic Factors and HRQoL at 6 Months

In the first step of the GLM-MANOVA, the association between the six RTOG toxicity scales and HRQoL at 6 months after completion of radiotherapy was investigated. Initially, the overall effect of each toxicity scale on the six HRQoL scales was investigated separately (one-factor model; Table 2). The same procedure was followed for the pretreatment characteristics. In this analysis, the combination of the four functioning scales, the global HRQoL scale, and the fatigue scale were used as the dependent variables. This analysis showed that four RTOG toxicity scales were associated significantly with overall HRQoL outcome (Table 2). Age and treatment modality also correlated significantly with HRQoL.

A multifactor model analysis was then performed in which the factors that were significantly associated with HRQoL outcome in the one-factor analysis were entered into the model. This analysis revealed two RTOG toxicity scales that significantly affected HRQoL, $RTOG_{xerostomia}$ and $RTOG_{swallowing}$. Age and treatment modality also remained significantly associated with HRQoL outcome at 6 months.

$RTOG_{xerostomia}$ and HRQoL Outcome

Statistically significant differences between patients with different grades of $RTOG_{xerostomia}$ were observed for all of the individual EORTC QLQ-C30 scales (Table 3). No clinically relevant differences were noted between grade 1 and grade 0 $RTOG_{xerostomia}$. In the case of grade 2 $RTOG_{xerostomia}$, little impact was observed on any of the HRQoL scales. In the case of grade 3 to 4 $RTOG_{xerostomia}$, a moderate impact was observed on emotional functioning and fatigue, and a large effect was observed on global quality of life (QOL) and social functioning.

Table 2. Results of the GLM Multivariate Analysis for Variance Testing the Overall Effect of RTOG Toxicity Scales and Prognostic Factors on the Six EORTC QLQ-C30 Scales

Independent Variable	One-Factor Model*				Multifactor Model†	
	Wilks' λ	F	*df*	*P*	Wilks' λ	*P*
RTOG late toxicity						
$RTOG_{xerostomia}$: grade 0 *v* 1 *v* 2 *v* 3-4	0.897	2.508	18	.001	0.948	.003
$RTOG_{mucosal}$: grade 0 *v* 1 *v* 2 *v* 3-4	0.923	1.822	18	.019	0.965	NS
$RTOG_{swallowing}$: grade 0 *v* 1 *v* 2 *v* 3-4	0.798	4.957	18	.001	0.859	.001
$RTOG_{subcutanuous}$: grade 0 *v* 1 *v* 2 *v* 3-4	0.922	1.821	18	.018	0.974	NS
$RTOG_{larynx}$: grade 0 *v* 1 *v* 2 *v* 3-4	0.934	1.478	18	NS	0.971	NS
$RTOG_{skin}$: grade 0 *v* 1 *v* 2 *v* 3-4	0.956	1.014	18	NS	0.984	NS
Other variables						
Sex: female *v* male	0.973	1.092	6	NS	0.973	NS
Age: 18-65 *v* > 65 years	0.950	3.943	6	.001	0.940	.001
UICC stage: I *v* II *v* III *v* IV	0.956	1.116	18	NN	0.983	NS
Primary tumor site: oral cavity *v* oropharynx/nasopharynx *v* larynx/hypopharynx	0.915	1.669	24	.022	0.969	NS
Treatment modality: RT alone *v* RT+CHT *v* S+RT	0.965	1.329	12	NS	0.945	.002

Abbreviations: GLM, general linear model; RTOG, Radiation Therapy Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; NS, not significant; UICC, International Union Against Cancer; RT, radiotherapy; CHT, chemotherapy; S, surgery.
*The one-factor model refers to the analysis in which only one independent variable was entered into the model.
†The multifactor model refers to the analysis in which initially all mentioned factors were entered as independent variables in the model (backward exclusion).

Table 3. Results of the Analysis of the Relationship Between the RTOG Toxicity Scales and the Observed Scores of the Individual EORTC QLQ-C30 Scales at 6 Months After Completion of Radiotherapy and the Clinical Relevance of the Differences Observed

Toxicity and HRQoL Scales	Mean Scores by Toxicity Grading														
	Grade 0		Grade 1				Grade 2				Grade 3-4				
	Mean	SD	Mean	SD	Cohen's D*	CR	Mean	SD	Cohen's D*	CR	Mean	SD	Cohen's D*	CR	*P*
$RTOG_{xerostomia}$															
No. of patients	113		159				152				19				
Physical functioning	80.9	19.1	82.3	19.4	0.07	No	74.7	18.5	0.33	S	71.2	21.0	0.48	S	.001
Role functioning	73.7	29.0	73.6	31.3	0.00	No	67.1	29.6	0.23	S	66.7	27.2	0.25	S	.044
Emotional functioning	83.8	18.6	80.2	23.1	0.17	No	73.7	25.8	0.45	S	69.3	25.8	0.64	M	.001
Social functioning	87.9	19.0	84.6	22.1	0.16	No	79.4	22.1	0.41	S	64.0	31.1	0.93	L	.001
Global quality of life	73.4	21.6	74.7	22.2	0.05	No	65.2	21.4	0.38	S	55.4	18.6	0.89	L	.001
Fatigue	25.4	24.3	28.3	24.1	0.11	No	36.3	24.3	0.45	S	42.1	20.8	0.74	M	.001
$RTOG_{swallowing}$															
No. of patients	163		143				46				64				
Physical functioning	84.0	17.2	81.6	17.0	0.14	No	72.0	18.1	0.68	M	67.8	19.8	0.87	L	.001
Role functioning	77.3	27.9	75.5	26.5	0.18	No	62.3	30.3	0.52	M	55.0	33.4	0.73	M	.001
Emotional functioning	84.0	20.2	80.0	23.1	0.18	No	69.9	24.6	0.63	M	68.8	25.2	0.67	M	.001
Social functioning	91.0	15.1	83.2	22.4	0.41	S	73.2	24.2	0.88	L	68.2	26.8	1.05	L	.001
Global quality of life	78.1	19.2	71.9	19.2	0.32	S	63.0	21.3	0.74	M	56.4	23.3	1.02	L	.001
Fatigue	23.1	22.1	29.3	21.9	0.28	S	40.8	24.0	0.77	M	42.5	25.4	0.81	L	.001

NOTE. Only the RTOG scales that were significantly associated with the HRQoL scales (Table 2) are mentioned.
Abbreviations: RTOG, Radiation Therapy Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; HRQoL, health-related quality of life; SD, standard deviation; CR, classification of the clinical relevance based on Cohen's D; No, no clinical relevance; S, small compared with grade 0; M, moderate compared with grade 0; L, large compared with grade 0.
*Cohen's D was calculated relative to grade 0.

$RTOG_{swallowing}$ and HRQoL Outcome

At 6 months after completion of radiotherapy, statistically significant differences between patients with different grades of $RTOG_{swallowing}$ were observed for all of the individual EORTC QLQ-C30 scales (Table 3). Small effects were observed for grade 1 $RTOG_{swallowing}$ on emotional and social functioning, global QOL, and fatigue. In the case of grade 2 $RTOG_{swallowing}$, moderate effects were observed on all scales except on social functioning, for which a large effect was observed. In

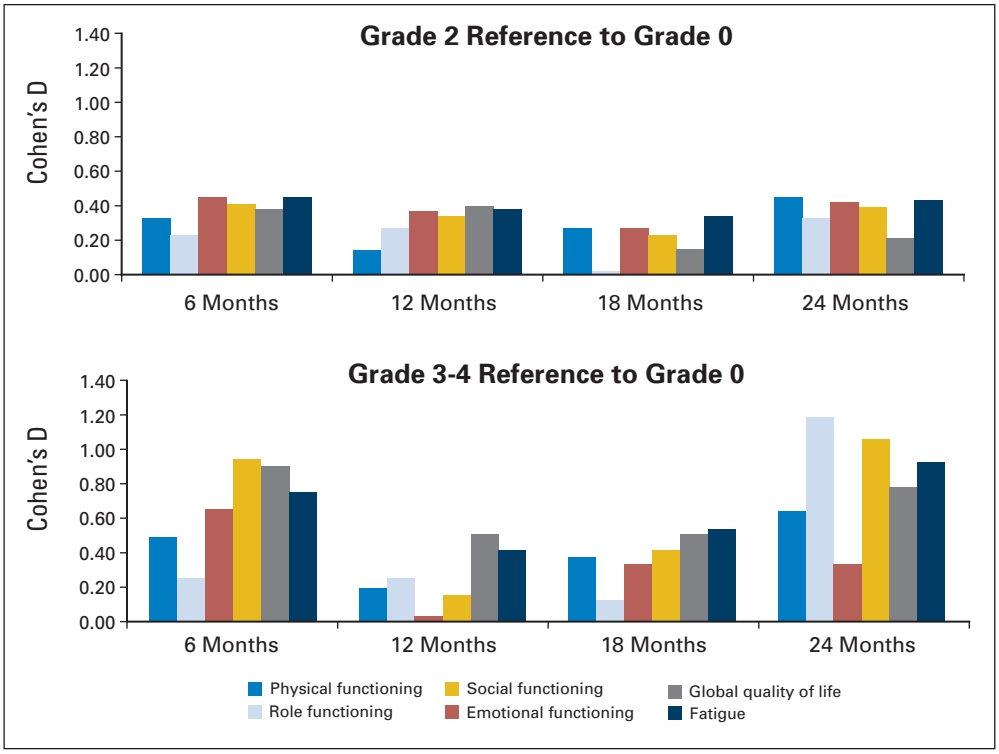

Fig 1. The magnitude of the effect of grade 2 $RTOG_{xerostomia}$ compared with grade 0 (3a) and grade 3 $RTOG_{xerostomia}$ compared with grade 0 on health-related quality of life as expressed by Cohen's D as a function of time. The magnitude of the effect was relatively low in the first 18 months after completion of radiotherapy but was increasing at 24 months. RTOG, Radiation Therapy Oncology Group.

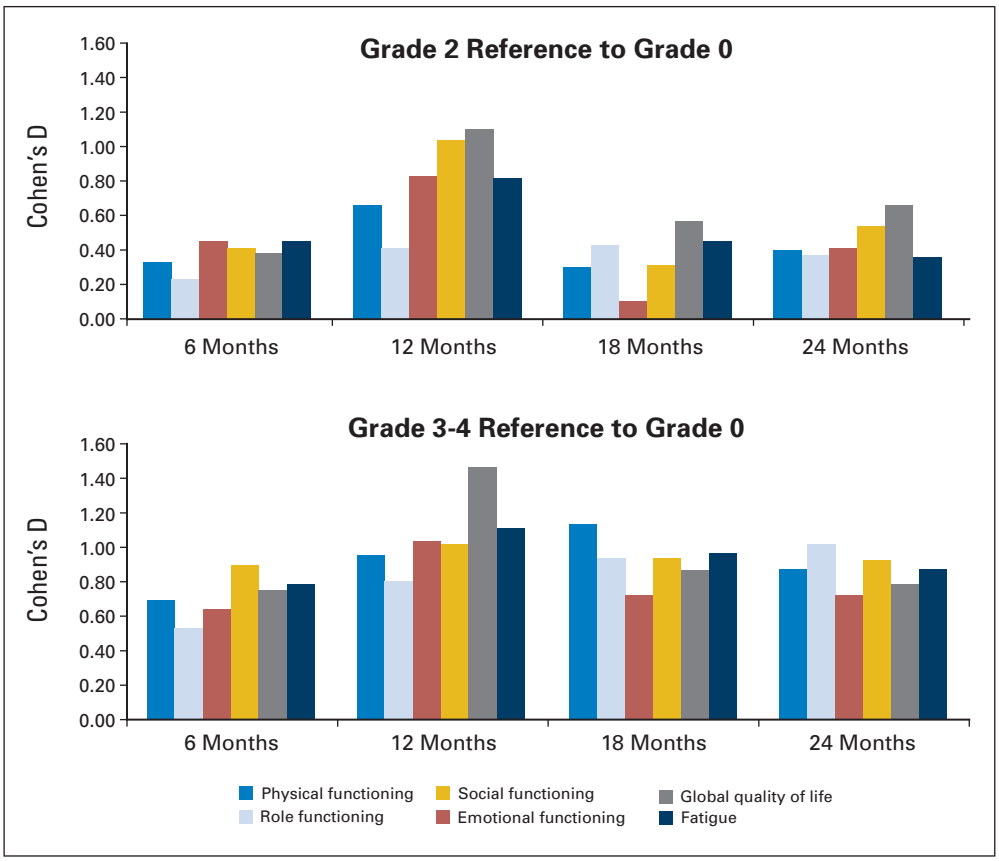

Fig 2. The magnitude of the effect of grade 2 $RTOG_{swallowing}$ compared with grade 0 (4a) and grade 3 $RTOG_{swallowing}$ compared with grade 0 on health-related quality of life as expressed by Cohen's D as a function of time. The magnitude of the effect was highest in the first 12 months after completion of radiotherapy and declined at 18 and 24 months. RTOG, Radiation Therapy Oncology Group.

the case of grade 3 to 4 $RTOG_{swallowing}$, large effects were observed on all HRQoL outcomes except for role and emotional functioning.

Changes Over Time

To investigate whether the impact of $RTOG_{xerostomia}$ and $RTOG_{swallowing}$ changed over time, the effect sizes for each of the HRQoL scales were calculated at 12, 18, and 24 months. The impact of $RTOG_{xerostomia}$ was relatively low in the first 18 months after completion of radiotherapy but gradually increased at 24 months (Fig 1). The impact of $RTOG_{swallowing}$ was highest in the first 12 months after completion of radiotherapy and gradually decreased at 18 and 24 months (Fig 2). The figures clearly show that $RTOG_{swallowing}$ had more impact on HRQoL than did $RTOG_{xerostomia}$ in the first 18 months after completion of radiotherapy. At 24 months, the impact of these two toxicities on HRQoL was similar.

DISCUSSION

The primary question posed in the current study is whether treatment-related adverse effects significantly affect a number of HRQoL dimensions that are considered particularly relevant for head and neck cancer patients. Results of the multivariate analysis indicated that two of the six RTOG morbidity scales investigated had a statistically significant and clinically relevant impact on self-reported HRQoL.

Radiation-induced xerostomia is generally considered to be the most frequently reported adverse effect after radiotherapy for head and neck cancer, and it is often assumed that xerostomia has a large impact on HRQoL. One of the most striking findings of the current study was that the impact of $RTOG_{xerostomia}$ on various HRQoL domains was less pronounced than that observed for $RTOG_{swallowing}$. This was particularly the case during the first 18 months after completion of radiotherapy. Similar results were recently reported by Jensen et al,[5] who performed a cross-sectional study among 116 recurrence-free head and neck cancer patients treated with radiotherapy. In that study, the correlation between physician-rated xerostomia and the HRQoL domains assessed by the EORTC QLQ-C30 was also less strong than that observed between other physician-rated toxicities (eg, dysphagia and hoarseness) and HRQoL.

The results of the current study indicate that $RTOG_{swallowing}$ has a major impact on patients' HRQoL. In particular, HRQoL was significantly affected by grade 3 or 4 toxicity (fluids only and tube feeding dependency, respectively). A number of other studies have also reported a similar impact of treatment-related dysphagia on HRQoL.[5,9,10] Although the incidence of grade 2 or higher $RTOG_{swallowing}$ is lower than that of $RTOG_{xerostomia}$, prevention of radiation-induced dysphagia might be even more important than prevention of radiation-induced xerostomia, particularly in the first 18 months after completion of radiotherapy. It is noteworthy that, even in the case of grade 1 $RTOG_{swallowing}$ toxicity, HRQoL is negatively affected. This hypothesis is supported by the findings of Kulbersh et al[11] who investigated the utility of pretreatment swallowing exercises in improving post-treatment swallowing and HRQoL. Patients who performed pretreatment swallowing exercises not only showed improvement in the

overall M.D. Anderson Dysphagia Inventory compared with a control population, but also demonstrated an improved HRQoL, including global HRQoL, and improvement on the emotional, functional, and physical domains. It should be noted that the incidence of swallowing problems after radiotherapy with or without chemotherapy differs considerably across studies, but most are higher than that reported in the present study.[11-14]

The question arises as to whether new radiation delivery techniques may contribute to improved HRQoL after radiotherapy by prevention of long-term radiation-induced dysphagia. In this regard, it becomes increasingly important to identify anatomic structures for which the dose distributions are significantly associated with swallowing problems. Eisbruch et al[15] reported high rates of swallowing problems after treatment among patients treated with radiotherapy and concomitant gemcitabine. They concluded that the most likely cause of post-treatment dysphagia was thickening of the pharyngeal constrictor muscles, the supraglottic larynx, and the glottic larynx. In addition, compared with three-dimensional conformal radiotherapy, moderate sparing of these structures was achieved by intensity-modulated radiotherapy (IMRT) without compromising target doses. Recently, Levendag et al[16] reported the results of a cross-sectional study of 81 patients with oropharyngeal cancer treated with three-dimensional conformal radiation therapy or IMRT. They found that the probability of swallowing complaints was significantly associated with the mean total dose in the superior and middle pharyngeal constrictor muscles. Jensen et al[17] reported on a small prospective study that investigated swallowing function after radiotherapy using functional endoscopic evaluation of swallowing and its correlation with irradiated volumes. Several significant correlations were found between both subjective and objective swallowing problems and dose volume histogram parameters of anatomic swallowing structures.

The results of the present study clearly indicate that radiation-induced morbidity has a significant impact on various HRQoL domains. Knowledge of these associations may contribute meaningfully to guiding the development of radiation delivery techniques that spare anatomic structures subject to radiation-induced morbidity. Currently, the development of new radiation techniques in head and neck cancer is focused primarily on sparing salivary gland tissue and reducing radiation-induced xerostomia. This focus is largely based on the results of a number of studies showing a clear relationship between the dose distributions in the salivary glands and the probability of reduced salivary flow and/or subjective xerostomia.[18-20] However, based on the results of the present study, it remains unclear whether a reduction in the incidence of xerostomia will translate into improved HRQoL. This is illustrated by a small prospective randomized study in which 51 patients with nasopharyngeal carcinoma were randomly assigned to receive conventional radiotherapy versus IMRT.[21] The results showed that IMRT was significantly better than conventional radiotherapy in terms of parotid sparing and salivary flow after radiotherapy. Patients treated with IMRT reported significantly better physical and role functioning as assessed by the EORTIC QLQ-C30, but no other differences in HRQoL were observed between the treatment arms. However, it should be emphasized that significant reductions in toxicity can still be meaningful, even if they are not always accompanied by concomitant improvement in self-reported HRQoL.

It should be noted that the RTOG scales have never been formally validated for inter-rater reliability. In that respect, the outcome of the current study helps to validate the global association between QOL changes with $RTOG_{xerostomia}$ and $RTOG_{swallowing}$.

Another limitation of this study is that only patients alive and free of recurrence were taken into account. It is obvious that patients with the most advanced tumors are more likely to develop tumor failure and less likely to survive. From this point of view, the results of this study may be biased because the more advanced patients are probably treated with larger volumes with a higher risk of radiation-induced adverse effects. However, the multivariate analysis, which only included the assessable patients, did not reveal major confounding.

Currently, there are no well-designed studies supporting therapeutic measures for swallowing problems after radiation treatment, although specific interventions to improve swallowing after radiation have been advocated.[22] Prevention in term of dose reduction in relevant anatomic structures may be a promising approach. However, more detailed and validated information on the relationship between the dose distributions in the anatomic structures and swallowing complaints is required. At our department, parotid-sparing IMRT is now applied on a routine basis. A prospective study on swallowing-sparing IMRT will be started soon.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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