

## Scientific Article

# Long-Term Aspects of Quality of Life in Head and Neck Cancer Patients Treated With Intensity Modulated Radiation Therapy: A 5-Year Longitudinal Follow-up and Comparison with a Normal Population Cohort



Edvard Abel, MD,<sup>a,\*</sup> Ewa Silander, PhD,<sup>b</sup> Jan Nyman, MD, PhD,<sup>a</sup>  
Thomas Björk-Eriksson, MD, PhD,<sup>a,c</sup> and Eva Hammerlid, MD, PhD<sup>b</sup>

<sup>a</sup>Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; <sup>b</sup>Department of Otorhinolaryngology-Head and Neck Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; and <sup>c</sup>Regional Cancer Centre West, Gothenburg, Sweden

Received 4 December 2018; revised 11 April 2019; accepted 17 July 2019

## Abstract

**Purpose:** Knowledge of long-term health-related quality of life (HRQOL) in patients with advanced head and neck cancer treated with intensity modulated radiation therapy is scarce.

**Methods and Materials:** HRQOL in 126 patients with advanced head and neck cancer treated with intensity modulated radiation therapy was followed longitudinally from diagnosis to 5 years after treatment with the European Organization for Research and Treatment of Cancer's QLQ-C30, the European Organization for Research and Treatment of Cancer's Head and Neck Cancer Module, and the M.D. Anderson Dysphagia Inventory. The survivors' HRQOL was compared with an age- and sex-matched normal population cohort.

**Results:** At 5 years, 73 of the 95 surviving patients had completed the study. Significant reductions in general pain (29 vs 12), head and neck (HN) pain (22 vs 14), and feeling ill (20 vs 10) were found, and emotional functioning (70 vs 83) and global quality of life (67 vs 74) improved, compared with baseline values. Conversely, dry mouth (19 vs 56), senses (8 vs 27), teeth problems (10 vs 22), opening mouth (19 vs 56), and sticky saliva (15 vs 40) were markedly worse, although significant improvements had occurred over time after treatment. Anderson Dysphagia Inventory scores >80 at 5 years indicated good swallowing function. In a subgroup analysis, dry mouth and senses were significantly better in patients treated with chemoradiotherapy. Comparison to a normal population cohort's HRQOL shows that the study group experienced a wide array of symptoms affecting their quality of life.

**Conclusions:** The results of this large, long-term follow-up study show that a majority of patients report a reasonable quality of life 5 years after treatment and that there seems to be continuous improvement over time. Comparison with a normal population cohort, however, underlines the

Sources of support: This work had no specific funding.

Disclosures: none.

\* Corresponding author: Edvard Abel, MD; E-mail: [edvard.abel@oncology.gu.se](mailto:edvard.abel@oncology.gu.se)

<https://doi.org/10.1016/j.adro.2019.07.015>

2452-1094/© 2019 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

fact that classical side effects remain, even with improved radiation techniques. Additional emphasis on normal-tissue-sparing radiation therapy is warranted, with close attention devoted to HRQOL outcomes.

© 2019 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Radiation therapy is a standard of care in advanced head and neck cancer (HNC). With high survival rates, it is important to follow the patients' health-related quality of life (HRQOL). Validated patient-reported outcome measures, such as the European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30 questionnaire, covering common symptoms, psychologic status, daily life functions, and other disease-specific aspects, are important tools.<sup>1</sup>

In the treatment of HNC, HRQOL typically deteriorates during radiation therapy. Although many parameters recover nearly to baseline values 1 year after treatment, long-term follow-up of patients treated with 3-dimensional conformal radiation therapy (3D-CRT) reveals long-lasting deterioration of xerostomia and dysphagia and related symptoms.<sup>2-4</sup>

The introduction of intensity modulated radiation therapy (IMRT) in the treatment of HNC has increased conformity of radiation doses to target volumes and increased avoidance of predefined organs at risk (OAR), such as the salivary glands and the pharyngeal musculature. This can potentially lead to improved HRQOL.<sup>5</sup> The HRQOL effects related to the introduction of IMRT have been investigated and compared with those of 3D-CRT in several studies, showing clear benefit, ie, less xerostomia and a possible improvement in swallowing function.<sup>6,7</sup> We recently reported potential beneficial effects in other HRQOL domains, such as pain, sexual function, cognitive function, and financial difficulties.<sup>8</sup> However, these are all short-term (up to 1-year follow-up) data. With a higher proportion of long-term survivors among HNC patients, it becomes important to assess long-term HRQOL outcomes.

This study aimed at evaluating long-term effects on HRQOL after IMRT by longitudinally following patients for at least 5 years and comparing to HRQOL before treatment. To evaluate the survivors' HRQOL, the data were compared with an age- and sex-matched cohort from the normal population, using the same quality of life questionnaires, QLQ-C30 and the Head and Neck Cancer Module.

## Methods and Materials

### Study design

Patients in the western part of Sweden with recently diagnosed HNC, who were referred to the regional

multidisciplinary tumor board for treatment recommendations, were asked to participate in the study. Only patients undergoing curative full-dose IMRT were included. They were followed up for 5 years after diagnosis. The HRQOL questionnaires were sent by mail and the patients were reminded once if they did not respond. Questionnaires were distributed at 4 time points: before starting treatment and at 1, 2, and 5 years after treatment. Patients were included between 2008 and 2010. The study was approved by the Regional Ethics Committee in Gothenburg.

### Radiation therapy

Radiation therapy was administered in doses respectively ranging from 64 to 72 Grays (Gy) to full-dose target volumes and from 40 to 52 Gy to adjuvant volumes. Accelerated fractionation schedules were used, either with 1.7 Gy per fraction given 10 times a week or 2 Gy per fraction given 6 to 8 times a week. During treatment planning, the highest priority was given to the spinal cord, with a maximum allowed dose of 46 Gy, followed by covering at least 95% of the primary target volume with 95% of the dose. The third priority was sparing the parotid glands, aiming at keeping mean doses below 26 Gy to the contralateral gland.<sup>9</sup>

### Chemotherapy

Induction (cisplatin and fluoruracil) or concomitant (weekly cisplatin) chemotherapy was added to the radiation therapy for patients with stage III to IV disease in accordance with local treatment standards at our department.

### Surgery

Patients with naso-, oro- or hypopharyngeal tumors were referred for definitive radiation therapy and surgery was thus not part of the initial treatment. Oral cavity tumors were surgically resected before radiation therapy unless they were considered technically inoperable. Radical modified neck dissection was performed in oral cavity patients with N-stage 1 to 3 disease and in patients with an unknown primary tumor, whereas patients with stage I to II oral cavity tumors underwent diagnostic neck dissection.

## HRQOL assessment

HRQOL data were assessed with 2 validated European Organization for Research and Treatment of Cancer (EORTC) instruments: the Core Questionnaire (QLQ-C30) and the Head and Neck Cancer Module (QLQ-HN-35).<sup>1,10,11</sup> The EORTC QLQ-C30 is a cancer-specific questionnaire containing a global quality of life score, 5 functional scales, 3 symptom scales and 6 single items. The QLQ-HN-35 contains 7 multiple-item and 6 single-item scales, assessing the HRQOL of HNC patients. Questionnaire scores were processed according to the EORTC scoring manual, yielding transformed scales ranging from 0 to 100.<sup>12</sup> High scores in the global and functional scales represent better functioning, although high scores in the symptom scales indicate problems. HRQOL scores of the survivors at 5 years were stratified in 5 groups (radiation therapy only vs added surgery, oropharyngeal vs nonoropharyngeal, stage I-II vs III-IV, added chemotherapy vs no chemotherapy and age <60 years vs > 60 years) for further analysis.

Additionally, the M. D. Anderson Dysphagia Inventory (MDADI) questionnaire was sent out at 5 years.<sup>13</sup> The MDADI consists of 20 questions, of which one is a global question, scored individually, to assess the overall effect of swallowing ability on quality of life. The remaining 19 items are divided into physical, emotional, and functional subscales that assess domain-specific performance. The composite MDADI score summarizes the overall responses in the remaining 19 items of the MDADI as a weighted average of the physical, emotional, and functional subscale scores. Composite and subscale scores are normalized to range from 20 (extremely low-functioning) to 100 (high-functioning).

Furthermore, some specific questions about the patients' current health (at 5 years) were added, including whether they had any new cancer or other severe disease, whether they experienced problems with their teeth or swallowing, and their opinion of their current weight.

## Reference scores in the normal population

To establish population-based norms for the EORTC QLQ-C30 and QLQ-HN-35, a random sample from the Swedish Population Register, representing the Swedish adult population, were asked to answer the questionnaires by mail. Of the 2200 invited, 1504 individuals responded, yielding QLQ-C30 results that were comparable to previously reported Swedish reference scores. The QLQ-HN-35 scores were relatively low, implying few head and neck-related problems in the normal population.<sup>14</sup> These reference scores were compared with those of the patients in the present study 5 years after completion of radiation therapy.

## Statistics

Study participants' and the normal population's HRQOL scores were compared using Fisher exact test for dichotomous variables, the Mantel-Haenszel  $\chi^2$  test for ordered categorical variables, and the Mann-Whitney *U* test for continuous variables. For comparison between 2 groups Fisher nonparametric permutation test was used for continuous variables. For comparison over time, the Wilcoxon signed-rank test was used for continuous variables. *P* values < .05 were considered statistically significant throughout. A difference between scores of 10 points or more was considered clinically significant.<sup>15</sup>

## Results

### Patients

One hundred and thirty-five patients were included in the study. Patient characteristics at inclusion are shown in [Table 1](#). The mean age was 60 years (range, 26-82) and the male-to-female ratio was roughly 3:1. The dominant tumor site was the oropharynx (*n* = 80), with the remaining cases distributed between oral (*n* = 16), the nasopharynx (*n* = 11), neck node metastases with unknown primary (*n* = 10), and the hypopharynx (*n* = 9). More advanced stages (stage III-IV) were predominant (*n* = 108). The 2- and 5-year survival rates were 86.5% and 75.4%, respectively.

### Compliance

The total number of responders at each time-point is displayed in [Table 2](#). Of the 135 patients included, 6 did not receive radiation therapy at all, one was changed from curative to palliative intent, one withdrew consent and one died during treatment, leaving 126 patients for evaluation. After 5 years, 95 of these 126 patients were still alive, of whom 73 (77%) completed the study. There were no significant differences in the distribution of sex, age, tumor site, stage, or additional treatment at baseline between the patients who finished the study and the 22 living patients who did not respond to the questionnaires.

### Treatment

The IMRT was administered either with a simultaneous-boost technique (*n* = 97) or with a sequential technique, with dose distribution plans (DDP) for all target volumes up to 40 Gy and a subsequent 3D-CRT boost to the full-dose target volume (*n* = 29).

## Parotid doses

The mean dose to the parotid gland contralateral to the primary tumor was 28.4 Gy in the 126 patients included in the study. In the 73 patients responding at 5 years, the mean dose was 27.4 Gy. There was a small difference in contralateral parotid dose between patients with IMRT-only DDPs and those with partial 3D-CRT DDPs (27.7 Gy and 25.3 Gy, respectively).

## EORTC QLQ-C30 and QLQ-HN-35

Table 3 shows the mean scores for each item at each time-point and the difference compared with baseline values. From the QLQ-C30, the physical functioning score decreased by 4 points (92 vs 88) between baseline and 5 years. Role functioning (78 vs 86) and emotional functioning (70 vs 83) increased by 8 and 13 points, respectively. The latter corresponded to a clinically relevant difference of more than 10 points. Diarrhea (8 vs 5) and financial difficulties (15 vs 10) exhibited small, but statistically significant, improvements, whereas pain showed a statistically and clinically significant reduction, that is, 17 points (29 vs 12). Likewise, from the QLQ-HN-35, head and neck pain (22 vs 14) and feeling ill (20 vs 10) scores decreased significantly, compared with baseline. Global quality of life increased from 67 to 74.

On the other hand, statistically significant increases in QLQ-HN-35 symptom scores at 5 years, compared with

**Table 2** Responders at each time point

Time point*	Responders	Patients alive
Inclusion	126	126
1 y	95	119
2 y	83	109
5 y	73	95

\* Time points represent time after initiation of treatment.

baseline values, were found in social eating (15 vs 20) and sexuality (24 vs 33). Furthermore, there were clinically relevant differences in problems with senses (8 vs 27), teeth (7 vs 27), opening mouth (10 vs 22), dry mouth (19 vs 56), and sticky saliva (21 vs 40). However, the last 2 items show significant improvements between 1 year and 5 years after treatment (ie, 9 and 8 points, respectively). Opening mouth and particularly problems with teeth, on the other hand, increased between 2 and five years after treatment (ie, 8 and 10 points, respectively).

Figure 1 shows the mean score at each time-point for items with statistically significant differences at 5 years, compared with baseline values.

## Stratified analysis

In patients treated with radiation therapy with or without surgery, oropharyngeal versus nonoropharyngeal, and stage I to II versus II to IV, no significant differences between the groups were seen. In Table 4 relative mean score changes from baseline to 5 years in the chemotherapy versus no chemotherapy and age under or over 60 years are shown. Significant increases of the mean score changes in the variables diarrhea (13, 3), senses (18, 1), and dry mouth (19, 5) were present in the no added chemotherapy group compared with patients treated with chemotherapy, suggesting a worsening of symptoms. The mean contra-lateral parotid doses to the chemo versus no-chemo groups were 28.7 versus 25.5 Gy. In the comparison between age groups, the decline in cognitive functioning was significantly worse in the younger age group (7, 9), whereas the opposite was found in social functioning (11, 4). The changes in global quality of life, general pain and feeling ill were all significantly higher in the younger patients, but these items were all significantly worse at baseline compared with the older age group. (Data not shown in the Table.)

## Comparison with normal population cohort

Mean EORTC QLQ-C30 and HN-35 scores in the study group at 5 years, compared with reference values in the normal population, are shown in Table 5. The cohort is age- and sex-matched with the study group (5 years were added to the baseline age in the study group).

**Table 1** Patient characteristics at baseline and at 5 years

	Patients included (n = 126)	Responders after 5 y (n = 73)
Sex		
Female	29 (23.0%)	18 (24.7%)
Male	97 (77.0%)	55 (75.3%)
Mean age	59.9 (10.2)	58.5 (9.9)
Tumor site		
Oral	16 (12.7%)	6 (8.2%)
Oropharynx	80 (63.5%)	52 (71.2%)
Hypopharynx	9 (7.1%)	1 (1.4%)
Nasopharynx	11 (8.7%)	7 (9.6%)
Unknown primary	10 (7.9%)	7 (9.6%)
Stage		
I	3 (2.4%)	2 (2.7%)
II	15 (11.9%)	10 (13.7%)
III	19 (15.1%)	10 (13.7%)
IV	89 (70.6%)	51 (69.9%)
Added chemotherapy	91 (72.2%)	52 (71.2%)
Primary surgery	10 (7.9%)	3 (4.1%)
Neck dissection	20 (15.9%)	11 (15.1%)
1-y survival	119 (94.4%)	
2-y survival	109 (86.5%)	
5-y survival	95 (75.4%)	

**Table 3** HRQOL scores in patients followed up for 5 years with differences compared with baseline at each time point

	Baseline	1 y		2 y		5 y	
	<i>n</i> = 73	<i>n</i> = 68		<i>n</i> = 67		<i>n</i> = 73	
	Mean score	Mean score	Δ BL to 1 y <i>P</i> value	Mean score	Δ BL to 2 y <i>P</i> value	Mean score	Δ BL to 5 y <i>P</i> value
<b>QLQ C-30</b>							
Physical functioning	92	89	.038	91	ns	88	.0047
Role functioning	78	81	ns	88	.016	86	.02
Emotional functioning	70	83	<.0001	85	<.0001	83	<.0001
Cognitive functioning	88	88	ns	87	ns	83	ns
Social functioning	83	85	ns	88	ns	85	ns
Global HRQOL	67	71	ns	77	.011	74	.039
Fatigue	24	23	ns	20	ns	23	ns
Nausea/vomiting	5	2	ns	1	ns	3	ns
Pain	29	16	.0052	13	.024	12	<.0001
Dyspnea	18	18	ns	14	ns	21	ns
Insomnia	26	19	ns	19	ns	18	ns
Appetite loss	14	16	ns	9	ns	15	ns
Constipation	8	7	ns	8	ns	10	ns
Diarrhea	8	4	ns	2	.039	5	ns
Financial difficulties	15	9	ns	6	ns	10	.029
<b>QLQ-HN-35</b>							
Head and neck pain	22	19	ns	19	ns	14	.010
Swallowing	16	17	ns	16	ns	18	ns
Senses	8	31	<.0001	27	<.0001	27	<.0001
Speech	11	11	ns	10	ns	13	ns
Social eating	15	22	.031	18	ns	20	ns
Social contacts	5	5	ns	4	ns	5	ns
Sexuality	24	24	ns	26	ns	33	.020
Dry mouth	19	65	ns	60	<.0001	56	<.0001
Coughing	21	17	ns	17	ns	20	ns
Teeth	7	16	.069	14	.031	27	<.0001
Opening mouth	10	20	<.0001	13	ns	22	.0013
Sticky saliva	15	48	<.0001	43	<.0001	40	<.0001
Feeling ill	20	10	.060	12	ns	10	.026

*Abbreviations:* Δ BL = change of mean score from baseline; HRQOL = health-related quality of life; ns = not significant. High score on function and global quality of life scale implies high function. High score on a symptom scale implies high level of problems. The maximum number of responders is represented at each time point.

Statistically significant differences favoring the normal population were found in social functioning (83 vs 90), loss of appetite (15 vs 3), constipation (10 vs 5), HN pain (14 vs 3), swallowing (18 vs 2), senses (27 vs 6), speech impairment (13 vs 6), social eating (20 vs 3), teeth (27 vs 9), opening mouth (22 vs 2), dry mouth (56 vs 12), and sticky saliva (40 vs 7). Global quality of life (74 vs 76) and fatigue (23 vs 19) did not, however, differ.

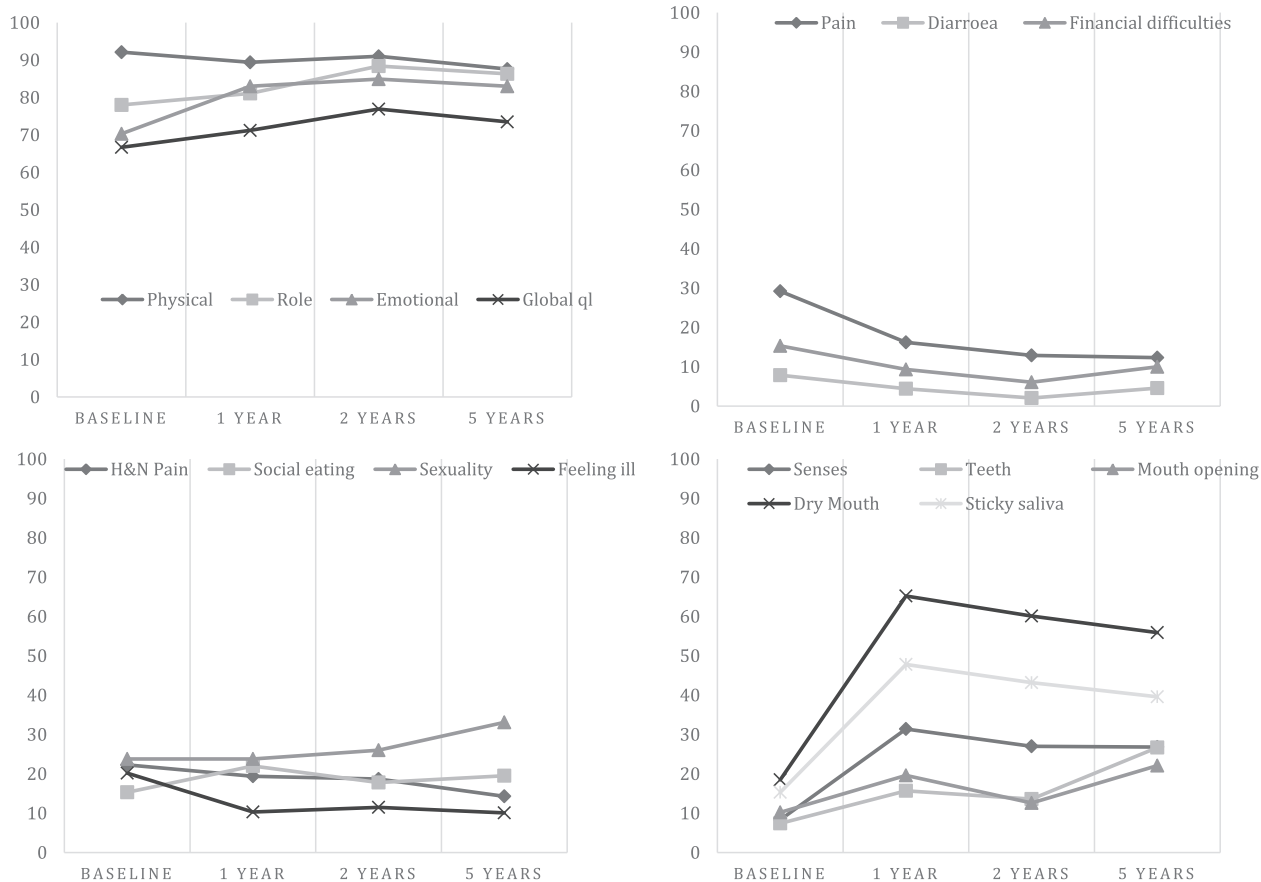
**MDADI and specific questions**

Seventy-three patients responded to the MDADI. Mean scores at 5 years were 80.3 for the global question, 80.1 for the composite scale, 80.8 for the physical subscale, 86.8 for the emotional subscale, and 87.7 for the functional subscale.

Regarding the specific questions asked at 5 years, 4 patients (5%) answered that they had been diagnosed with a new cancer, 52 (71%) were content with their current weight, and 19 (26%) and 23 (31%), respectively, reported problems with their jaws or teeth. Eight patients (11%) experienced constriction when swallowing and one patient (1%) had undergone dilatation of the esophagus.

**Discussion**

This is, to our knowledge, one of the larger long-term follow-up studies of the effects on HRQOL in patients treated with IMRT for HNC. We found a reduction in pain and feeling ill and an improvement in global quality of life compared with baseline values. Previous smaller studies have shown similar results in some scores but not



**Figure 1** Mean score at each timepoint for items with statistically significantly different score at 5 years compared with baseline values.

all. In a retrospective study by Chen et al, 50 long-term survivors treated with IMRT for HNC were evaluated at 3 and 5 years posttreatment.<sup>16</sup> They reported that a majority of patients (84%) had better HRQOL than at the time of diagnosis. Because that analysis was retrospective in a selected patient group (eg, patients with laryngectomy or tracheostomy were excluded), extensive conclusions cannot be drawn. Vainshtein et al report outcomes up to 6.5 years after swallowing- and salivary-organ-sparing IMRT in 69 patients with stage III or IV oropharyngeal cancer.<sup>17</sup> They found stable and improved HRQOL compared with before treatment in most domains, but also an unexpected worsening of HN pain and overall bother in the long term compared with 2 years after treatment. In an observational, cross-sectional study, Huang et al assessed HRQOL in 242 patients (142 IMRT and 100 non-IMRT) 5 years after treatment for nasopharyngeal cancer.<sup>18</sup> Global quality of life, cognitive functioning, social functioning, fatigue, and 11 head-and-neck-specific items were found to be statistically and clinically in favor of the IMRT group. Because these were exclusively patients with nasopharyngeal cancers, it would be precarious to draw specific conclusions about other HNC sites.

Dysphagia is a well-known long-term side effect of radiation therapy for HNC. It is therefore noteworthy that swallowing, assessed with the EORTC QLQ-HN-35, seems to be unaffected, with equal scores at all time points in this study. In a long-term ( $\geq 10$  years) randomized trial comparing weekly intra-arterial cisplatin in combination with definitive radiation therapy to standard chemoradiation, Kraaijenga et al reported better HRQOL scores for dysphagia, trismus, and speech impairment in patients treated with IMRT.<sup>19,20</sup> Their study did not focus primarily on radiation therapy technique because IMRT was introduced during the trial’s timeline. Therefore, only a small number of IMRT patients were evaluated ( $n = 22$ ). To further evaluate the perceived effect of swallowing dysfunction, the patients in our study were asked to respond to the MDADI, yielding mean scores  $>80$  for all scales, which is generally regarded as indicating high function.<sup>21</sup> To interpret these data, a recent publication from Goepfert et al, in which 46 patients with low- to intermediate-risk oropharyngeal cancer treated with definitive IMRT were followed up for up to 2 years, provides useful background. They found mean MDADI scores (composite score 83.1 at 24 months) similar to those in

**Table 4** Mean score changes from baseline to 5 years in 2 different subgroups

	Chemotherapy <i>n</i> = 52	No chemotherapy <i>n</i> = 21	Age <60 y <i>n</i> = 30	Age >60 y <i>n</i> = 43
	Mean score change from baseline to 5 years			
<b>QLQ C-30</b>				
Physical functioning	−4.2*	−5.4	−6.2 <sup>†</sup>	−3.4
Role functioning	6.9	11.1	13.8	4.3
Emotional functioning	11.9 <sup>‡</sup>	13.9 <sup>†</sup>	12.9 <sup>†</sup>	12.2 <sup>‡</sup>
Cognitive functioning	−5.9	−2.4	−9.8 <sup>§</sup>	−1.5
Social functioning	1	1.6	8.62	−3.1 <sup>§</sup>
Global HRQOL	7.2 <sup>†</sup>	6	14.2 <sup>‡</sup>	1.7 <sup>§</sup>
Fatigue	0	0.5	−1.9	1.6
Nausea/vomiting	−1.6	−0.8	−3.5	0
Pain	−14.7 <sup>†</sup>	−21.4 <sup>†</sup>	−25.3 <sup>†</sup>	−10.9 <sup>†,§</sup>
Dyspnea	6.5	−4.8	4.6	2.3
Insomnia	−7.8	−7.9	−10.3	−6.2
Appetite loss	−0.7	3.2	2.3	−0.8
Constipation	3.9	−1.6	−1.2	4.7
Diarrhea	−6.5*	4.8 <sup>§</sup>	−6.9	−0.8
Financial difficulties	−5.2	−4.8	−6.9	−3.9
<b>QLQ-HN-35</b>				
Head and neck pain	−6.3	−9.9	−10.1	−5.7
Swallowing	4.8	−4.7	−5.1	6.6
Senses	13.6 <sup>‡</sup>	31.7 <sup>‡,§</sup>	12.5*	23.4 <sup>‡</sup>
Speech	2.7	2.1	1.9	2.9
Social eating	3.7	4.4	−1.7	7.7
Social contacts	−0.4	−0.6	0.9	−1.4
Sexuality	9.5*	6.7	3.7	11.9*
Dry mouth	31.3 <sup>‡</sup>	50.8 <sup>‡,§</sup>	35.7 <sup>‡</sup>	38.1 <sup>‡</sup>
Coughing	−2	1.6	−5.9	2.4
Teeth	18.1 <sup>‡</sup>	22.2 <sup>†</sup>	18.5 <sup>†</sup>	19.8 <sup>‡</sup>
Opening mouth	10.9*	15.9	5.9	16.7 <sup>‡</sup>
Sticky saliva	23.1 <sup>‡</sup>	26.3 <sup>†</sup>	17.3*	28.5 <sup>‡</sup>
Feeling ill	−8.7	−12.7	−19.8*	−3.3 <sup>§</sup>

Abbreviation: HRQOL = health-related quality of life.

For changes within group: \**P* < .05, <sup>†</sup>*P* < .01, and <sup>‡</sup>*P* < .001. For changes between groups: <sup>§</sup>*P* < .05. Positive changes on function and global quality of life scales imply better function. Positive changes on symptom scales imply worse problems.

our study.<sup>22</sup> However, taking into account normal population scores and the fact that around 10% of patients reported some sort of swallowing problems in response to the specific questions, IMRT for sparing pharyngeal musculature might potentially reduce the long-term symptoms. A randomized phase III trial focusing on this issue is currently ongoing.<sup>23</sup>

A stratified analysis was added, addressing the heterogeneity of the included patients. No significant differences in mean score changes were found in patients with added surgery, with different tumor sites or stages, possibly owing to few patients in some of the groups. There were, however, significant higher scores in reported xerostomia and taste alteration in the group that received no chemotherapy compared with those with chemoradiation. There were no significant differences in the baseline QOL scores between the groups and the mean parotid doses were approximately the same which

otherwise could have been a possible explanation to this finding. It is believed that the combination of chemoradiotherapy should aggravate symptoms compared with radiation therapy alone, even though there are few studies directly addressing this.<sup>24</sup> This finding should therefore be investigated further in future randomized trials.

The targeted mean dose to the contralateral parotid gland, <26 Gy, could not be reached in all patients and the score for dry mouth was markedly increased at 5 years. Hawkins et al followed 252 patients for up to 5 years and correlated mean salivary gland doses to responses to a xerostomia-specific questionnaire, finding a high correlation between lower parotid, submandibular and oral cavity doses and better questionnaire scores.<sup>25</sup> They reported the lowest rates of patient-reported xerostomia when doses to both parotid glands were kept below 26 Gy. These findings are somewhat limited by the

**Table 5** HRQOL scores, IMRT compared with normal-population cohort

	IMRT 5 years ( <i>n</i> = 73)	Normal population ( <i>n</i> = 530)	<i>P</i> value
Sex			
Female	18 (24.7%)	132 (24.9%)	
Male	55 (75.3%)	398 (75.1%)	1.00
Age mean (lowest; highest)	63.5 (31.0; 81.0)	63.5 (41.0; 85.0)	0.97
QLQ C-30			
Physical functioning	87.6	89.4	ns
Role functioning	86.3	87.1	ns
Emotional Functioning	83.0	85.3	ns
Cognitive functioning	82.9	86.5	ns
Social functioning	84.5	89.7	0.044
Fatigue	23.4	18.8	ns
Nausea/vomiting	3.2	2.8	ns
Pain	12.3	17.1	ns
Dyspnea	21.0	16.2	ns
Insomnia	18.3	16.2	ns
Appetite loss	14.8	3.2	<.0001
Constipation	10.0	4.9	ns
Diarrhea	4.6	4.7	ns
Financial difficulties	10.0	6.0	ns
Global QoL	73.5	76.0	ns
QLQ-HN-35			
Head and neck pain	14.3	2.6	<.0001
Swallowing	17.8	2.0	<.0001
Senses	26.8	5.6	<.0001
Speech	13.1	5.7	<.0001
Social eating	19.5	2.6	<.0001
Social contacts	5.1	3.6	ns
Sexuality	33.1	25.2	ns
Problems with teeth	26.7	9.4	<.0001
Opening mouth	22.1	1.7	<.0001
Dry mouth	55.9	12.1	<.0001
Sticky saliva	39.6	6.7	<.0001
Coughing	19.7	16.5	ns
Feeling ill	10.1	11.0	ns

Abbreviations: HRQOL = health-related quality of life; IMRT = intensity modulated radiation therapy; ns = not significant; QoL, quality of life.

fact that a low proportion of surviving patients (22%) completed the questionnaire at 5 years. Nevertheless, better sparing of the parotid glands would most likely have improved the scores at 5 years in our study. Additionally, sparing the submandibular glands and their lubricating function is also important in reducing xerostomia, but they were not prioritized OAR.<sup>26</sup> The mandible and teeth were not prioritized OAR either in our study.

Interpreting HRQOL data is often challenging; measuring HRQOL in the general population can thus provide useful background information when analyzing long-term effects.<sup>27</sup> Comparisons with normal population data have been made for other cancer diagnoses, but few concern HNC.<sup>28</sup> Our results clearly show that many head-and-neck-specific symptoms persist in the treated group, such as dry mouth, taste alteration, problems with teeth, and sticky saliva, but the effect on global quality of

life is less evident. Continuing emphasis on reducing adverse effects of radiation therapy in the head and neck region is crucial in giving long-term survivors a quality of life comparable to that of the rest of the population.

One possible limitation to this study is that we do not know why 22 living patients did not respond to the questionnaires at 5 years. There is a possibility that patients with worse HRQOL may be overrepresented in this group, which could have produced worse scores. The overall response rate (77%), however, is still satisfying. Owing to limited dose-planning resources at the start of the study, 22 patients (30%) of the 73 patients responding at 5 years were given IMRT combined with 3-dimensional CRT. This might have had an effect on the overall study results. However, the mean parotid doses did not seem to be affected by the choice of method.

In conclusion, we think that this study is one of the first and largest with long-term follow-up of HRQOL in



patients treated with IMRT for advanced HNC. The results imply that a majority of patients have a reasonable quality of life 5 years after treatment and that there seems to be continuing improvement over time. The comparison to a reference cohort from the normal population, however, still underlines the fact that, even with improved radiation techniques, the classic side effects remain. Optimizing dose plans, taking OAR constraints into account, with technical developments such as proton therapy and adaptive radiation therapy, should further emphasize the sparing of normal tissues, leading to better HRQOL outcomes.

## Acknowledgments

The distribution and administration of the health-related quality of life questionnaires and input of the resultant data were funded by grants from Västra Götalandsregionens regionala forskningsfond (Region Västra Götaland's regional research fund). The sponsors were not involved in the design of the study or in the writing of the manuscript.

## References

- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365-376.
- Hammerlid E, Silander E, Hörnrestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer—A longitudinal study. *Head Neck.* 2001;23:113-115.
- Jellema AP, Slotman BJ, Doornaert P, et al. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2007;69:751-760.
- Epstein JB, Robertson M, Emerton S, Phillips N, Stevenson-Moore P. Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. *Head Neck.* 2001;23:389-398.
- Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: Promises and pitfalls. *J Clin Oncol.* 2006;24:2618-2623.
- Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. *Lancet Oncol.* 2011;12:127-136.
- Vergeer MR1, Doornaert PA, Rietveld DH, et al. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: Results of a nonrandomized prospective study using a standardized follow-up program. *Int J Radiat Oncol Biol Phys.* 2009;74:1-8.
- Abel E, Silander E, Nyman J, et al. Impact on quality of life of IMRT versus 3-D conformal radiation therapy in head and neck cancer patients: A case control study. *Adv Radiat Oncol.* 2017;2:346-353.
- Eisbruch A, Dawson LA, Kim HM, et al. Conformal and intensity modulated irradiation of head and neck cancer: The potential for improved target irradiation, salivary gland function, and quality of life. *Acta Otorhinolaryngol Belg.* 1999;53:271-275.
- Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer.* 2000;36:1796-1807.
- Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol.* 1999;17:1008-1019.
- Fayers PM, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. botEQoL Group. *The EORTC QLQ-C30 Scoring Manual.* 3rd ed. European Organisation for Research and Treatment of Cancer; 2001.
- Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: The M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg.* 2001;127:870-876.
- Hammerlid E, Adnan A, Silander E. Population-based reference values for the European Organization for Research and Treatment of Cancer Head and Neck module. *Head Neck.* 2017;39:2036-2047.
- King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res.* 1996;5:555-567.
- Chen AM, Daly ME, Farwell DG, et al. Quality of life among long-term survivors of head and neck cancer treated by intensity-modulated radiotherapy. *JAMA Otolaryngol Head Neck Surg.* 2014;140:129-133.
- Vainshtein JM, Moon DH, Feng FY, et al. Long-term quality of life after swallowing and salivary-sparing chemo-intensity modulated radiation therapy in survivors of human papillomavirus-related oropharyngeal cancer. *Int J Radiat Oncol Biol Phys.* 2015;91:925-933.
- Huang TL, Chien CY, Tsai WL, et al. Long-term late toxicities and quality of life for survivors of nasopharyngeal carcinoma treated with intensity-modulated radiotherapy versus non-intensity-modulated radiotherapy. *Head Neck.* 2016;38(Suppl 1):E1026-E1032.
- Kraaijenga SA, Oskam IM, van Son RJ, et al. Assessment of voice, speech, and related quality of life in advanced head and neck cancer patients 10-years+ after chemoradiotherapy. *Oral Oncol.* 2016;55:24-30.
- Kraaijenga SA, Oskam IM, van der Molen L, et al. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. *Oral Oncol.* 2015;51:787-794.
- Hutcheson KA, Barrow MP, Liseac A, et al. What is a clinically relevant difference in MDADI scores between groups of head and neck cancer patients? *Laryngoscope.* 2016;126:1108-1113.
- Goepfert RP, Lewin JS, Barrow MP, et al. Long-term, prospective performance of the MD anderson dysphagia inventory in "low-intermediate risk" oropharyngeal carcinoma after intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2017;97:700-708.
- Petkar I, Rooney K, Roe JW, et al. DARS: A phase III randomised multicentre study of dysphagia- optimised intensity-modulated radiotherapy (Do-IMRT) versus standard intensity- modulated radiotherapy (S-IMRT) in head and neck cancer. *BMC Cancer.* 2016;16:770.
- Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: A systematic review. *Oral Oncol.* 2014;50:254-262.
- Hawkins PG, Lee JY, Mao Y, et al. Sparing all salivary glands with IMRT for head and neck cancer: Longitudinal study of patient-reported xerostomia and head-and-neck quality of life. *Radiother Oncol.* 2018;126:68-74.
- Wang ZH, Yan C, Zhang ZY, et al. Impact of salivary gland dosimetry on post-IMRT recovery of saliva output and xerostomia grade for head-and-neck cancer patients treated with or without

- contralateral submandibular gland sparing: A longitudinal study. *Int J Radiat Oncol Biol Phys.* 2011;81:1479-1487.
27. Fayers PM. Interpreting quality of life data: Population-based reference data for the EORTC QLQ-C30. *Eur J Cancer.* 2001;37:1331-1334.
28. Schaake W, de Groot M, Krijnen WP, Langendijk JA, van den Bergh AC. Quality of life among prostate cancer patients: A prospective longitudinal population-based study. *Radiother Oncol.* 2013;108:299-305.