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ABSTRACT

Background: The aims were to determine health-related quality of life (HRQoL), including voice problems, dysphagia, depression, and anxiety after total laryngectomy (TL), and investigate the associations between HRQoL and the late effects.

Methods: Cross-sectional study including 172 participants having received TL 1.6-18.1 years ago for laryngeal/hypopharyngeal cancer who filled in the EORTC QLQ-C30, EORTC QLQ-H&N35, V-RQOL, MDADI, and HADS questionnaires.

Results: Participants scored worse than normative reference populations on all scales/items of the EORTC questionnaires, except one, and almost half of the scales/items showed a clinically relevant difference. Moderate/severe dysphagia was present in 46%, moderate/severe voice problems in 57%, depression in 16%, and anxiety in 20%. Decreasing age, increasing numbers of comorbidities, increasing voice problems, increasing dysphagia, and increasing depression symptoms, were associated with a lowered EORTC QLQ-C30 summary score.

Conclusion: A substantial proportion of participants experienced clinically significant late effects and increasing levels of these were associated with a lowered HRQoL.

Level of evidence: 3.

INTRODUCTION

Laryngeal and hypopharyngeal cancer patients treated with total laryngectomy (TL) are at risk of many late effects since the majority, in addition to the surgery, have received radiotherapy (RT), or chemoradiation. The most frequent known late effects after TL are voice problems (66%-84%)[1,2], dysphagia (35%-89%)[3], depression (23-33%)[4,5] and anxiety (8-32%)[4,5], all with a potential to impact health-related quality of life (HRQoL). Patient-reported outcome measures (PROMs) have become the mainstay in the evaluation of HRQoL and the most frequently used in the evaluation of TL patients are The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core and Head and Neck module (EORTC QLQ-C30, EORTC QLQ-H&N35)[6]. Evaluation of voice problems, dysphagia, depression, and anxiety after TL are done by PROMs but also by e.g. acoustic outcomes and fiberoptic endoscopic examination of swallowing (FEES) and a variety of PROMs are used to describe late effects after TL. HRQoL and late effects after TL therefore depends on how they are measured but also on when they are measured, since previous studies have found them to deteriorate right after laryngeal or hypopharyngeal cancer treatment only to stabilize after approximately one year[7,8].

A recently published systematic review investigating HRQoL after TL identified numerous studies on the subject but concluded that the strength of evidence was weak as many studies were of small sample size and poor quality[6]. In addition, only few studies have investigated the late effects associations with HRQoL following TL. They found that voice[2] and dysphagia[9] were associated with HRQoL but only in univariate analyses which do not take into account confounders, and possible interactions between variables. This in combination with the fact that associations between dysphagia and voice problems[1] and between dysphagia and depression or anxiety[10] have been found, makes it evident that multivariate analysis is needed to examine the associations between the different late effects and HRQoL. To our knowledge, no such analysis has been made for the TL population.

The primary aims of this population-based cross-sectional study were to determine patient-reported HRQoL and the occurrence of voice problems, dysphagia, depression, and anxiety after TL for laryngeal or hypopharyngeal cancer and to investigate the associations between HRQoL and the late effects in a multivariate analysis.

We hypothesized that voice problems, dysphagia, depression, and anxiety after TL are frequent and that each late effect is independently associated with HRQoL.

MATERIALS AND METHODS

Participants and data collection

This cross-sectional population-based questionnaire study included all surviving patients from Denmark and the two Swedish regions Västra Götaland and Skåne, who had received a TL following laryngeal or hypopharyngeal cancer between January 2000 and December 2015. In Denmark, the participants were identified through The Danish Health Data Authority[11] and in Sweden through the hospital databases.

All participants were invited by mail. Those not responding within 1 month were sent a reminder. The questionnaire contained questions on socio-demography (education and cohabitation status), lifestyle (smoking status and weekly alcohol consumption), comorbidities, speech rehabilitation method as well as the following five validated questionnaires:

EORTC QLQ-C30 is a general cancer questionnaire[12]. A high score on the functional scales, the global QoL scale, and the summary score indicates good functioning, whereas a high score on the symptom scales indicates a high level of symptoms.

EORTC QLQ-H&N35 is a head and neck cancer-specific questionnaire[13]. A high score indicated a high symptom burden. For both of the EORTC questionnaires, raw scores are linearly transformed to a scale of 0-100[14].

The Voice-Related Quality of Life questionnaire (V-RQOL)[15,16] is a voice specific questionnaire. Raw scores are linearly transformed to a scale of 0-100, a high score indicating good functioning.

The M.D. Anderson Dysphagia Inventory (MDADI)[17] is a dysphagia specific questionnaire. Raw scores are linearly transformed to a scale of 20-100, a high score indicating good functioning.

The Hospital Anxiety and Depression Scale (HADS)[18] is composed of two subscales; depression and anxiety. The score range is 0-21 for both scales and the score may be divided into three categories; normal (0-7), mild case (8-10), or case (11-21).

For responders, in case of ≥ 5 missing questionnaire items, the participants were sent an additional letter encouraging them to respond to the items. Missing items in the EORTC QLQ-C30 and

EORTC QLQ-H&N35 were handled according to the official scoring manual[14]. For the remaining questionnaires, no official recommendations for the handling of missing items exist. Missing items were calculated as the mean value of the remaining items of the subscale from the same participant, but only if a minimum of 50% of items in the subscale had been answered[19].

The remaining participant, tumor, and treatment characteristics were collected through participants' medical records as well as in Denmark through the DAHANCA (The Danish Head and Neck Cancer Group) database[20].

Treatment and rehabilitation

The primary standard of care treatment for squamous cell carcinoma of the larynx and hypopharynx in Denmark and Sweden is RT in combination with concurrent chemotherapy in the case of stage III-IV disease. Primary surgery can be used for early-stage laryngeal tumors (endoscopic laser resection) and laryngeal T4 tumors (TL). In Sweden, TL for T4 laryngeal tumors is used as standard primary treatment and in Denmark in selected cases, both in combination with postoperative RT.
During our study period, no nationally standardized rehabilitation program after TL has existed and therefore rehabilitation of our study population has not been uniform among regions. Also, rehabilitation has changed considerably during the study period, from practically no focus on rehabilitation to recommendations that all patients should be referred for general rehabilitation in their local municipality (Denmark) or at the hospital (Sweden[21]) following hospital discharge. Each rehabilitation plan is individual but can encompass occupational therapists, physiotherapists, and dietitians according to needs. Additionally, Danish and Swedish TL patients are referred regionally for specialized speech rehabilitation by a speech-language therapist.

Statistical analysis

Statistics were performed using SPSS for Mac (version 26; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to characterize sociodemographic and clinical variables. For questionnaire scores mean and SD, as well as group proportions, were used. The scores of the EORTC questionnaires were compared with male normative reference populations[22,23]. Normative data for the EORTC QLQ-C30 from a Danish population was used since over 2/3 of the study population were from Denmark. Normative data for the EORTC QLQ-H&N35 from Sweden was used since there exist no Danish reference scores for this questionnaire. Male reference data was chosen since over 3/4 of the study population were male. MCID values (minimally clinically important difference) calculated on oral cavity and oropharynx cancer patients were used to define a clinically relevant difference in scores[24]. These are calculated individually for each scale/item and vary between 6 and 15 with the far majority in the range of 8-12 points.

No official recommendations exist for the quantification of the degree of late effect severity for the chosen questionnaires. For the V-RQOL and MDADI questionnaires, based on their 5-point Likert scales, scores were divided into the following two groups: A score of ≥ 75 (V-RQOL) and ≥ 80 (MDADI) indicates a mild burden of symptoms and a score < 75 (V-RQOL) and < 80 (MDADI) indicates a moderate/severe symptom burden. For the V-RQOL mild symptom burden corresponds to the answers “non, not a problem” and “a small amount” and for the MDADI corresponds to the answers “strongly disagree” and “disagree”.

For the HADS questionnaire a cutoff ≥ 8 for both HADS-D and HADS-A has been shown to have the optimal balance between specificity and sensitivity as an indication of clinical depression or anxiety[25].

Odds ratio (OR) for having a depression depending on the number of moderate/severe late effects were calculated using multivariate logistic regression analysis and adjusting for sex (male vs. female), age (continuous), cohabitation status (living alone vs. living with a partner), and comorbidities (continuous).

For the multivariate analysis, we used a general linear model to investigate associations between HRQoL (EORTC QLQ-C30 summary score, continuous) and voice problems (V-RQOL total score, continuous), dysphagia (MDADI total score, continuous), depression (HADS-D, continuous), and anxiety (HADS-A, continuous) as well as the sociodemographic variables, sex (male vs. female), age (continuous), cohabitation status (living alone vs. living with a partner), and the number of comorbidities (continuous). Tests were considered statistically significant if $p < 0.05$.

Ethical considerations

The study was approved by the Danish Data Protection Agency, the Danish Health and Medicines Authority, and The Swedish Ethical Board **(**Dnr 2017/869**)**. Written informed consent was obtained from all participants.

RESULTS

We identified 244 people and received 172 replies, resulting in a response rate of 70%. Participants had a mean age of 71.4 years (range 43-91), were a median of 6.3 years (range 1.6-18.1) after TL, were predominantly male and almost half had <10 years of education. Most were former or current smokers, about 2/3 had comorbidity and the vast majority used tracheoesophageal (TE) speech. The most prevalent treatment modality was RT followed by salvage TL (67%) with a total radiation dose of 66-68 Gray (78%). Eleven percent had a recurrence of their laryngeal/hypopharyngeal cancer or diagnosis of another cancer type at time of questionnaire completion (Table 1 and 2).

Questionnaire results

Table 3 presents the mean scores of the EORTC QLQ-C30 and QLQ-H&N35 from the study population compared with normative reference scores. The study population scored worse on all

scales and items, except for the EORTC QLQ-C30 pain. When applying the MCID values, 13 of the scales/items (46%) showed a clinically important difference to the normative reference population with the largest differences found for senses problems (43), speech problems (26), dyspnea (23), and teeth (20).

Based on the total scores of the MDADI and V-RQOL questionnaires, moderate/severe dysphagia was present in 46% of participants and moderate/severe voice problems were present in 57% of participants (Figure 1-2).

According to the HADS questionnaire, 7% of participants were categorized as mild depression and 9% as depression while corresponding proportions were 12% and 8% for anxiety (Figure 3).

The adjusted OR for depression (score ≥ 8) was 4.4 (95% CI 1.56, 12.32) among participants who had moderate/severe voice problems and moderate/severe dysphagia compared with having only one of these late effects to a moderate/severe degree (Table 4). We could not include having no (0) moderate/severe late effects, as out of the 54 participants with no moderate/severe late effects, none were categorized as having a depression. See supplementary material for the mean scores from the V-RQOL, MDADI, and HADS questionnaires.

Late effects impact on HRQoL

The multivariate model was found to explain 69% (R^2) of the variance in the EORTC QLQ-C30 summary score in our population and found that decreasing age, increasing numbers of comorbidities, decreasing V-RQOL total score, decreasing MDADI total score, and increasing HADS-D score, all independently were associated with the EORTC QLQ-C30 summary score. Sex, cohabitation status, and HADS-A were not statistically significantly associated with the EORTC QLQ-C30 summary score (Table 5).

The variables with the highest parameter estimates were comorbidities, where an increase of 1 comorbidity was associated with a decline of 1.74 in the EORTC QLQ-C30 summary score, and

HADS-D, where a 1 score increase, was associated with a 1.26 decline in the EORTC QLQ-C30 summary score.

DISCUSSION

In this population of survivors after TL, we found a worse HRQoL compared with normative reference populations and also that clinically relevant problems of dysphagia, voice difficulties, depression, and anxiety were prevalent.

We chose to use sex-specific normative data, but not age-specific. This choice was based on the fact that our study population were almost evenly divided in three age groups (60-69, 70-79, and 80-90 years). If we, however, had chosen to use sex and age specific normative data (males, 70-79 years) we find that, in our study population, 9 instead of 13, scales and items had mean scores clinically relevantly worse than the normative reference population (leaving out physical functioning, role functioning, sexuality, and sticky saliva).

To our knowledge, the studies in the literature with the most comparable inclusion criteria as well as patient and treatment characteristics are by Lundström et al.[2], Arenaz Búa et al.[1], and Danker et al.[5] investigating respectively, 43, 45, and 193 non-selected laryngectomized patients operated consecutively in their regions in the periods 1988-2005, 2000-2016, and 1986-approximately 2007. Lundström et al. reported very similar results to ours in the EORTC questionnaires except for the H&N35 scales senses problems, teeth, dry mouth, and sticky saliva presenting mean scores between 9.8 and 17.1 points worse than our population. Since their population had been laryngectomized as early as 1988 an explanation for the higher symptom scores could therefore be that the participants had received a higher total radiation dose on a larger radiation field. When comparing results from the study group with mean scores from normative reference populations for the EORCT questionnaires using MCID values, a clinically important difference was found in 3 of the functional scales and 10 of the symptoms scales/items, indicating a suboptimal health status after

TL rehabilitation. In a study by Hammerlid et al., the HRQoL of 133 head and neck cancer patients 3 years after treatment was investigated[23,26]. The patients were diagnosed with cancer of several different head and neck subsites and 95% had received RT. In this study comparable HRQoL to an age and gender-matched normative reference population was found, even though statistically and clinically worse head and neck specific symptom-specific scores were found for 6 of the scales. Our population of only TL patients, however, had clinically relevant worse e.g. swallowing, senses problems, speech problems, and coughing problems than the head and neck cancer reference populations, which could be why our study population's HRQoL did not adjust as successfully.

Lundström et al., by use of the voice handicap index (VHI)[27], found a higher prevalence of voice problems (84%) and Arenaz Búa et al., by use of the VHI-T, report that 66% had a moderate/severe voice problem, which is in line with our results. The VHI is another commonly used voice questionnaire and the VHI and V-RQOL questionnaires have in a study by Franic et al.[28], evaluating the psychometric properties of voice disorder quality of life instruments, been appointed the psychometrically strongest of the assessed instruments. We chose the V-RQOL over the VHI due to the lower number of questions.

Arenaz Búa et al. also found that 89% had a swallowing problem which is higher than our findings. This could perhaps be attributed to their use of the Sydney Swallow Questionnaire[29]. This questionnaire is a functional health status questionnaire that quantifies the symptomatic severity of dysphagia as experienced by the patients and therefore does not measure the exact same thing as a HRQoL dysphagia questionnaire, such as the MDADI[30].

Danker et al. found the proportion of depression and anxiety in their population to be 33% and 32% respectively, which is higher than our findings. Their HADS cut-off points were, however, one point lower than ours, which could partly explain the higher frequencies than found in our study.

Late effects impact on HRQoL

The multivariate analysis found that decreasing age, increasing number of comorbidities, and increasing levels of voice problems, dysphagia, and depression, all independently were associated with a lowered HRQoL, measured by the EORTC QLQ-C30 summary score. To our knowledge, this study is the first to investigate associations between HRQoL and late effects after TL in a multivariate analysis and our findings supports not only our hypothesis but also previously found univariate associations between HRQoL and voice problems[2] and dysphagia[9], and the common perception that each late effect, except anxiety, is independently associated with HRQoL.
The summary score is a relatively new score presented in 2016 by Giesinger et al. on behalf of the EORTC Quality of Life Group[31]. One could argue whether the use of the summary score might challenge the clinical interpretation of the results, as it has pooled 13 of the 15 scales into one summary score. Giesinger et al. however argue that the original 15 outcomes of the questionnaire might generate a high risk of a type I error because of multiple testing. A summary score as a supplement to the original 15 scales was therefore constructed. Giesinger et al. found that it presents better or equal known groups validity and responsiveness compared with the individual EORTC QLQ-C30 scales and most recently Husson et al. showed that the summary score had a stronger prognostic value for overall survival among a mixed cancer population than any of the original EORTC QLQ-C30 scales[32]. Another possibility would have been to have used the EORTC QLQ-C30 global QoL scale. This scale, however, only consists of 2 questions and therefore perhaps is too insensitive. Additionally, the global QoL scale has been found to be more susceptible to response shift than the other scales in the questionnaire[33] and a recent systematic review[6], investigation HRQoL after total laryngectomy, found that the global QoL scale only was clinically important different from the normative reference population in eight out of 19 included studies.

Rehabilitation of the late effects investigated in our study has received different levels of attention in the literature. Voice rehabilitation techniques have been thoroughly studied and report TE speech to be superior to electrolaryngeal and esophageal speech[34]. However, despite 79% of our study

population reporting TE speech as their primary mode of communication, 57% still had a moderate/severe voice problem.

Rehabilitation of dysphagia after TL has recently been examined in a systematic review[3]. The studies investigated different surgical treatments (dilatation, and laser resection of pseudodiverticulum), Botulinum Toxin A injections, and coping strategies. The authors concluded that the results were promising but that no statistically significant treatment results were found. RT is, however, besides TL another known risk factor for the development of dysphagia, and is part of many TL patients' treatment regimen. Cochrane recently published a systematic review including 6 RCTs with 326 advanced-stage head-and-neck cancer participants but found no effect on post-treatment swallowing function of swallowing exercise before, during, or after treatment[35]. With the current lacking evidence for dysphagia rehabilitation, focus on minimization of the occurrence of dysphagia by swallowing-sparing RT[36], and TL operation technique (e.g. choice of flap reconstruction[37] and selection of pharyngeal closure technique[38]) is of even more importance.

Occurrence and treatment of depression and anxiety after TL have received little attention in the literature. We found depression and anxiety to be frequent in our population and in addition, found a more than four-fold increased OR for depression among participants with both moderate/severe voice problems and moderate/severe dysphagia compared with having either-or. Singer et al.[4] found that only a fraction of the participants identified with depression or anxiety after TL in their study had ever received psychiatric or psychotherapeutic treatment. Possible explanations for this could be the patients dissimulating their symptoms or that the medical personnel is not aware that the burden of dysphagia and voice problems may increase the risk of mental disorders as a late effect after TL.

Medical personnel in contact with TL patients should, in addition to the focus on voice problems and dysphagia, be extra aware of possible psychological late effects of clinical relevance, especially when both a voice problem and dysphagia are present.

Strengths and limitations

The strengths of the study are the high number of participants compared with previous studies on the subject, the high response rate, and the low frequency of missing items in both questionnaires, and demographics. An additional strength is the use of multivariate analysis in analyzing late effects associations with HRQoL, as well as having adjusted for important confounders.

The limitations of the study are the cross-sectional study design, thereby not being able to show causality, the heterogeneity in rehabilitation regimes, and the potential survival and non-response bias, both possibly leading to an overestimation of HRQoL and underestimation of late effects. Also, although the sample size is large, it still precluded further analyses of associations with HRQoL i.e. over time since TL and cancer at time of questionnaire completion.

CONCLUSION

In this population-based study of HRQoL and late effects after TL for laryngeal or hypopharyngeal cancer, we found that patients after TL had a worse HRQoL compared with normative reference populations. Clinically relevant problems with dysphagia, voice difficulties, depression, and anxiety were prevalent and increasing levels of these late effects, except anxiety, were associated with a lowered HRQoL. In the future, the focus should be on minimizing the occurrence and improving the treatment of the late effects voice problems, dysphagia, depression, and anxiety.

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Figure titles and legends

Figure 1. Participants V-RQOL scores grouped by late effect severity

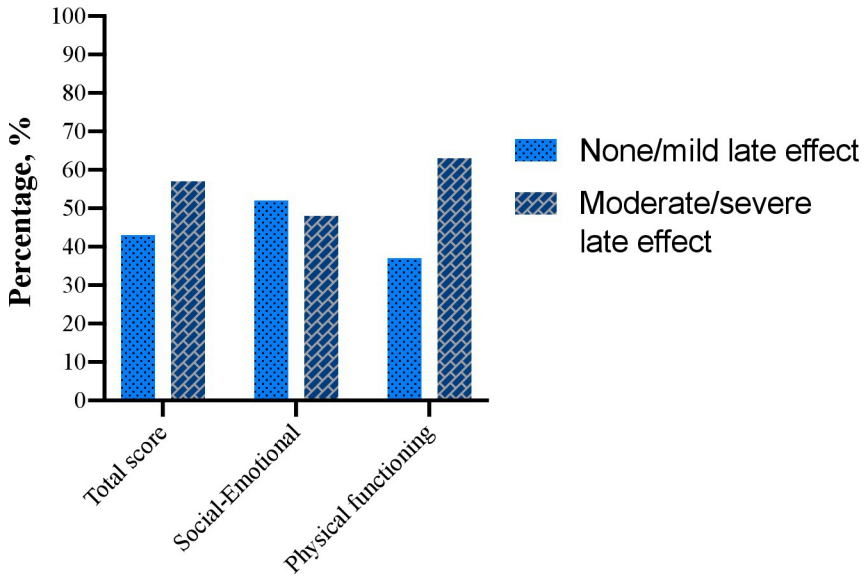
V-RQOL: The Voice-Related Quality of Life questionnaire
None/mild late effect: Score ≥ 75
Moderate/severe late effect: Score < 75

Figure 2. Participants MDADI scores grouped by late effect severity

MDADI: The M.D. Anderson Dysphagia Inventory
None/mild late effect: Score ≥ 80
Moderate/severe late effect: Score < 80

Figure 3. Participants HADS scores grouped by caseness

HADS: The Hospital Anxiety and Depression Scale
HADS-D: The Hospital Anxiety and Depression Scale, depression
HADS-A: The Hospital Anxiety and Depression Scale, anxiety
Normal: score 0-7
Mild case: score 8-10
Case: score 11-21



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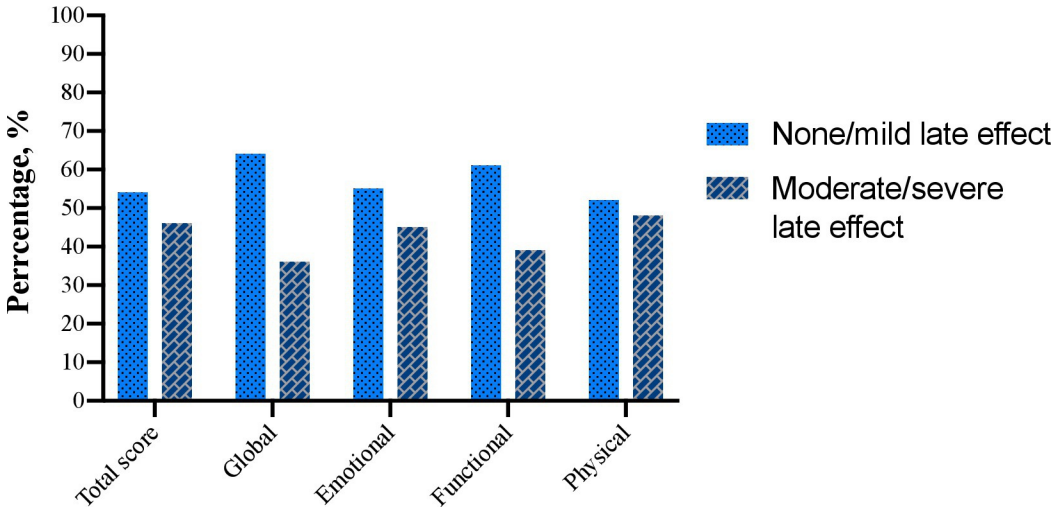

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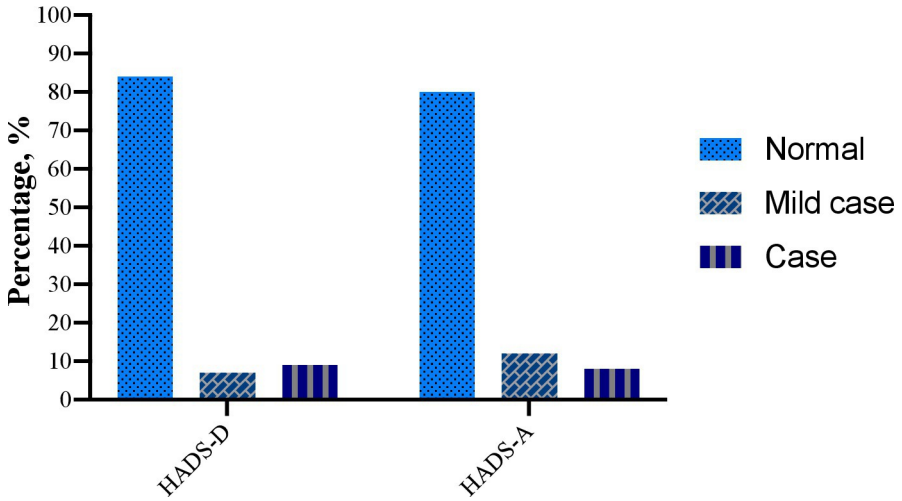

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Table 1. Participant characteristics at the time of questionnaire completion

Variables	No. (%)
Sex	
Male	147 (85)
Female	25 (15)
Age, years (in mean and SD)	71.4 (9.9)
Cohabitation status	
Married or cohabitating	104 (60)
Single, divorced/separated, or widower/widow	68 (40)
Level of education, years	
< 10: primary or lower secondary school	84 (49)
10-12: upper secondary school or vocational education	44 (26)
> 12: higher education	43 (25)
Not specified	1 (1)
Smoking status	
Current smoker	10 (6)
Former smoker	145 (84)
Never smoker	16 (9)
Not specified	1 (1)
Weekly alcohol consumption*	
Abstainers	55 (32)
Below high-risk consumption	93 (54)
Above high-risk consumption	21 (12)
Not specified	3 (2)
Comorbidities, no. †	
0	64 (37)
1-2	82 (47)
3-5	26 (15)
Speech rehabilitation method	
Tracheoesophageal speech	136 (79)
Esophageal speech	11 (6)
Electrolaryngeal speech	16 (9)
No voice restoration	9 (5)
Laryngeal or hypopharyngeal cancer disease status	
Disease-free	169 (98)
Recurrence	3 (2)
Other cancer	
No	156 (91)
Yes	16 (9)
Present oncological treatment	
No cancer	153 (89)
No oncological treatment for current cancer	15 (9)
Chemotherapy	3 (2)
Chemoradiation	1 (1)
Time since TL, years (median and range)	6.3 (1.6-18.1)

***** As recommended by the Danish National Board of Health: Below risk consumption is defined as ≤ 14 units (women) or 21 units (men) per week. High-risk consumption is defined as > 14 units (women) or 21 units (men) per week.

† Heart failure, heart attack, stroke, type 1 diabetes, type 2 diabetes, chronic lung disease, ulcer, liver disease, arthritis, metabolic disease, atrial fibrillation, scleroderma, tinnitus, psoriasis, trigeminal neuralgia, Parkinson, depression, anxiety, and cancer.

Table 2. Tumor and treatment characteristics at primary diagnosis

Variables	No. (%)
Tumor site	
Hypopharynx	5 (3)
Subglottis	3 (2)
Glottis	114 (66)
Supraglottis	41 (24)
Transglottis	2 (1)
Chondrosarcoma	7 (4)
Histology	
Squamous cell carcinoma	153 (89)
Other than squamous cell carcinoma	17 (10)
Not specified	2 (1)
T stage	
T1	47 (27)
T2	63 (37)
T3	34 (20)
T4	18 (11)
Chondrosarcoma	7 (4)
Not specified	3 (2)
N stage	
N0	141 (82)
N1	9 (5)
N2	15 (9)
Chondrosarcoma	7 (4)
M stage	
M0	165 (96)
Chondrosarcoma	7 (4)
Treatment modality	
TL alone*	15 (9)
TL and postoperative radiotherapy	22 (13)
Radiotherapy and salvage TL	116 (67)
Chemoradiation and salvage TL	9 (5)
Radiotherapy and salvage TL and postoperative chemotherapy	1 (1)
CO2-laser and salvage TL†	1 (1)
CO2-laser, radiotherapy, and salvage TL	7 (4)
Partial laryngectomy and salvage TL‡	1 (1)
Total radiation dose (pre- or postoperative), Gray	
< 66	28 (18)
66-68	120 (77)
> 68	2 (1)
Not specified	5 (3)
Country of total laryngectomy surgery	
Denmark	118 (69)
Sweden	54 (32)

TL: total laryngectomy

* 6 had previously received radiotherapy for former head and neck cancer and therefore were unable to receive any more irradiation, 6 had chondrosarcoma, 1 had another type of sarcoma, 1 had rhabdomyosarcoma, and 1 had claustrophobia

† participant with atypical histiocytoma

‡ participant with chondrosarcoma

Table 3. EORTC questionnaire scores (mean and SD) from the current study of 172 participants after TL and male normative reference populations

	Participants' mean (SD)	Normative reference mean (SD)[20,21]
EORTC QLQ-C30		
Summary score	78 (16)	
Global health status/QoL	65 (25)	73 (23)
Functional scales		
Physical functioning*	75 (21)	87 (21)
Role functioning*	70 (31)	83 (28)
Emotional functioning	78 (25)	85 (19)
Cognitive functioning	83 (22)	86 (20)
Social functioning*	74 (27)	89 (23)
Symptom scales/items		
Fatigue	32 (25)	23 (24)
Nausea and vomiting	6 (15)	3 (10)
Pain	14 (23)	21 (26)
Dyspnea*	35 (33)	12 (23)
Insomnia	25 (32)	19 (27)
Appetite loss	16 (27)	7 (18)
Constipation	12 (22)	5 (15)
Diarrhea	12 (22)	7 (17)
Financial difficulties	14 (27)	6 (18)
EORTC QLQ-H&N35		
Pain	7 (12)	3 (9)
Swallowing*	20 (24)	2 (7)
Senses problems*	48 (31)	5 (14)
Speech problems*	31 (27)	5 (13)
Trouble with social eating*	19 (28)	3 (8)
Trouble with social contact*	15 (22)	4 (11)
Less sexuality*	34 (40)	17 (29)
Teeth*	28 (38)	8 (19)
Opening mouth	9 (21)	1 (7)
Dry mouth	20 (28)	10 (21)
Sticky saliva*	24 (31)	7 (17)
Coughing*	32 (32)	16 (24)
Felt ill	14 (23)	12 (22)
Pain killers	38 (49)	
Nutritional supplements	14 (34)	
Feeding tube	5 (22)	
Weight loss	11 (32)	
Weight gain	20 (40)	

EORTC QLQ-C30: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core
EORTC QLQ-H&N35: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck
* Scales and items in which the study population had mean scores clinically importantly worse compared to the normative reference populations using MCID values

Table 4. Multivariate* adjusted odds ratio for being a mild case or case of depression†

	Odds Ratio	95% CI	p
Age‡	1.0	0.95, 1.04	0.862
Sex (male vs. female)	1.1	0.32, 3.74	0.882
Cohabitation status (living alone vs. living with a partner)	0.7	0.27, 1.90	0.709
Comorbidities‡	1.4	0.97, 1.99	0.075
Number of moderate/severe late effects (1 vs. 2)§	4.4	1.56, 12.32	0.005

* Multivariate: Logistic regression analysis

† Mild case or case of depression: HADS-D ≥ 8

‡ Continuous variable

§ Moderate/severe late effects: Moderate/severe voice problem (V-RQOL total score < 75), moderate/severe dysphagia (MDADI total score < 80)

Table 5. Multivariate analysis* of the associations between HRQoL†‡ and sociodemographics, and late effects variables

	Parameter estimate§	95% CI	p
Age‡	0.158	0.03, 0.29	0.016
Sex (male vs. female)	-0.024	-3.89, 3.84	0.990
Cohabitation status (living alone vs. living with a partner)	-0.428	-3.40, 2.55	0.777
Comorbidities‡	-1.735	-3.02, -0.45	0.008
V-RQOL total score‡	0.192	0.11, 0.28	0.000
MDADI total score‡	0.159	0.06, 0.26	0.002
HADS-D‡	-1.263	-2.01, -0.51	0.001
HADS-A‡	-0.30	-0.94, 0.35	0.363

***** General linear model

† HRQoL: Health-related quality of life, measured by the EORTC QLQ-C30 summary score

‡ Continuous variable

§ The change in the summary score associated with a one-unit increase of the variable, all other variables being held constant