Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises

Kraaijenga, S.A.C.; van der Molen, L.; Jacobi, I.; Hamming-Vrieze, O.; Hilgers, F.J.M.; van den Brekel, M.W.M.

DOI
10.1007/s00405-014-3379-6

Publication date
2015

Document Version
Final published version

Published in
European Archives of Oto-Rhino-Laryngology

Eur Arch Otorhinolaryngol (2015) 272:3521–3531
DOI 10.1007/s00405-014-3379-6

HEAD AND NECK

Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises

Sophie A. C. Kraaijenga · Lisette van der Molen · Irene Jacobi · Olga Hamming-Vrieze · Frans J. M. Hilgers · Michiel W. M. van den Brekel

Received: 29 August 2014 / Accepted: 25 October 2014 / Published online: 8 November 2014

Abstract Concurrent chemoradiotherapy (CCRT) for advanced head and neck cancer (HNC) is associated with substantial early and late side effects, most notably regarding swallowing function, but also regarding voice quality and quality of life (QoL). Despite increased awareness/knowledge on acute dysphagia in HNC survivors, long-term (i.e., beyond 5 years) prospectively collected data on objective and subjective treatment-induced functional outcomes (and their impact on QoL) still are scarce. The objective of this study was the assessment of long-term CCRT-induced results on swallowing function and voice quality in advanced HNC patients. The study was conducted as a randomized controlled trial on preventive swallowing rehabilitation (2006–2008) in a tertiary comprehensive HNC center with twenty-two disease-free and evaluable HNC patients as participants. Multidimensional assessment of functional sequels was performed with videofluoroscopy, mouth opening measurements, Functional Oral Intake Scale, acoustic voice parameters, and (study specific, SWAL-QoL, and VHI) questionnaires. Outcome measures at 6 years post-treatment were compared with results at baseline and at 2 years post-treatment. At a mean follow-up of 6.1 years most initial tumor-, and treatment-related problems remained similarly low to those observed after 2 years follow-up, except increased xerostomia (68 %) and increased (mild) pain (32 %). Acoustic voice analysis showed less voicedness, increased fundamental frequency, and more vocal effort for the tumors located below the hyoid bone ($n = 12$), without recovery to baseline values. Patients' subjective vocal function (VHI score) was good. Functional swallowing and voice problems at 6 years post-treatment are minimal in this patient cohort, originating from preventive and continued post-treatment rehabilitation programs.

Keywords Head and neck cancer · Chemoradiotherapy · Dysphagia · Swallowing · Voice · (Preventive) rehabilitation exercises

This paper was selected for an ORAL PRESENTATION at the IFHNOS World Congress & AHNS Annual Meeting in New York City (July 2014).

S. A. C. Kraaijenga · L. van der Molen · I. Jacobi · F. J. M. Hilgers · M. W. M. van den Brekel (✉)
Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
e-mail: m.vd.brekel@nki.nl

O. Hamming-Vrieze
Department of Radiation Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

F. J. M. Hilgers · M. W. M. van den Brekel
Institute of Phonetic Sciences, University of Amsterdam, Spuistraat 210, 1012 VT Amsterdam, The Netherlands

M. W. M. van den Brekel
Department of Oral and Maxillofacial Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Introduction

Organ preservation protocols with concurrent chemoradiotherapy (CCRT) are increasingly used for primary treatment of locally advanced head and neck cancer (HNC). Meta-analytic data from randomized controlled trials (RCTs) show improved loco-regional control and overall survival advantages for these protocols as compared to radiotherapy (RT) alone [1], but also higher

incidence of dysphagia secondary to CCRT-induced tissue reactions such as mucositis, fibrosis, neuropathies, and especially xerostomia [2, 3]. Both acute and long-term swallowing problems can result in decreased oral intake and eventually may lead to weight loss and (prolonged) nasogastric or percutaneous feeding tube dependency. Furthermore, dysphagia can adversely affect compliance to treatment and post-treatment recovery (e.g., because of aspiration problems), and can deteriorate patient's social contacts and quality of life (QoL) [3]. Since radiation fields frequently encompass the larynx, also substantial effects on voice quality have been noted, which are correlated to the RT dose to the larynx [4–6]. Combination with chemotherapy aggravates these negative effects on patients' speech, daily life activities, and again QoL [7–13].

Regarding dysphagia in the HNC field, many centers have made attempts to prevent or reduce swallowing sequels following CCRT. So far, focus primarily has been on reduction of the dose on pharyngeal musculature with advanced RT treatment planning techniques such as intensity-modulated radiation therapy (IMRT) [14–18]. More recently, pre-, per- and post-treatment interventions ensuring continued use of swallowing musculature by adherence to targeted swallowing exercises (the 'use it or lose it' concept) are increasingly suggested in the literature to benefit HNC survivors [19]. Preventive rehabilitation programs have been associated with a long list of positive effects: improved QoL [20], better base of tongue retraction and better maintained epiglottic inversion [21], superior muscle maintenance and functional swallowing ability [22], better oral intake and clinician-rated swallowing function at three and 6 months [23], reduced extent and severity of penetration and/or aspiration, less trismus, less weight loss, and less pain (both short term [24] and at one- and two-years post-treatment [25]), and better oral intake and shorter duration of feeding tube dependency [26] post-treatment. Also maintained oral intake (no feeding tube dependency) has been shown to lead to better swallowing function after CCRT, possibly due to continued use of the swallowing musculature [26–28]. Benefits from preventive (swallowing) exercises have been reported in particular on the short term (up to 2 years) [19]. Eisbruch et al. [29] were among the first prospectively evaluating swallowing function in HNC survivors, and these authors found objective swallowing dysfunction (high incidence of silent aspiration) 6–12 months after RT. Also Goguen et al. [30] described dysphagia to be only partly resolved 6–12 months following RT treatment. Nguyen et al. reported on somewhat longer term dysphagia severity following CCRT. After a median post-treatment follow-up of 17 months, severe dysphagia was found in 45 % of patients [31], whereas after more than 2 years post-treatment (median follow-up 26 months), it worsened in 20 % of patients [32]. More recently, Hutcheson et al. retrospectively evaluated dysphagia in HNC patients, who were treated more than 5 years ago. Aspiration and pharyngeal residue were the norm in all patients. Eighty-six percent had developed aspiration pneumonia and 66 % were tube feeding dependent as a consequence of their dysphagia [33]. Ackerstaff et al., and Metreau et al., evaluated long-term (5 years) results in advanced (stage IV) HNC patients following CCRT too. While Metreau et al. retrospectively assessed a high rate of dysphagia-related morbidity (feeding tube, oral supplements, and pneumonia) and QoL alterations, the prospective study of Ackerstaff et al. found QoL issues after 5 years follow-up to be similar to those at 1 year. A limitation of these latter two studies is that no objective evaluation of swallowing function was performed in these studies regarding long-term functional/QoL evaluation following CCRT. Moreover, none of these patient groups was treated with preventive (swallowing) exercises before, during, and/or after the course of treatment, whereas especially a prospective evaluation of swallowing therapy in the HNC population would be valuable/informative [3].

Regarding voice problems following (CC)RT for HNC, efforts to prevent or reduce sequels following treatment are scarcer. Furthermore, only few studies with adequate pre-treatment data collection prospectively investigated changes in patient- and observer-rated voice quality [6, 9–11, 34–36]. Longest follow-up was a year in all. Adequately controlled and randomized data on voice outcomes are scarce anyway, and the available studies often used different diagnostic tests to assess voice quality. Voice problems after (CC)RT treatment may be attributed to impaired vocal fold vibration with incomplete closure, as a result of dryness of the laryngeal mucosa, muscle atrophy, fibrosis, hyperemia, and erythema [8, 37]. As a result, abnormal acoustic and aerodynamic measures (harmonics-to-noise ratio, fundamental frequency, measures of jitter, shimmer, and spectral tilt) have been demonstrated in irradiated HNC patients. Also subjective voice problems, often assessed with the Voice Handicap Index (VHI), are reported in the available but limited literature on this topic [6, 38–42].

Earlier, we reported about the one- and two-year CCRT-related functional outcomes from a previous prospective RCT, comparing two preventive swallowing rehabilitation regimens [25]. In comparison with the literature, swallowing problems were limited in both treatment arms. Here, the prospectively collected objective and subjective functional swallowing and voice outcomes of this study in the combined patient cohort still alive at 6 years will be reported.

Materials and methods

This study concerns the long-term follow-up of all disease-free and evaluable patients from an original cohort of 55 patients with advanced (stage III and IV), functionally [43] or anatomically inoperable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx, who were treated with concurrent chemo-radiotherapy (CCRT) [24, 25, 44]. Of the original patient cohort of 55 patients, 49 patients actually completed treatment. Each patient received 100 mg/m^2 Cisplatin as a 40 min IV infusion on days 1, 22, and 43. Intensity-modulated RT (IMRT) of 70 Gy in 35 fractions was administered over seven weeks starting concurrently with chemotherapy. Of the 22 evaluable patients (see below) 20 (91 %) received a radiation dose of 43.5 Gy or higher to the larynx, because of advanced stage of the tumors and/or positive lymph nodes [45].

The original study compared two preventive rehabilitation programs (consisting of standard logopaedic swallowing exercises or an experimental swallowing rehabilitation program, based on the TheraBite® Jaw Motion Rehabilitation System™) [23]. Patients were instructed to practice daily from the start of treatment until 1 year post-treatment. Since both treatment groups showed more or less similar results, except for a slight but significant weight increase at 2 years with the experimental program [28], here the 6 years data of all disease-free and evaluable patients ($n = 22$) are combined. Of the additional seven patients included in the 2 years assessment ($n = 29$), in the meantime three had died, three suffered from severe unrelated disease precluding their participation in this long-term evaluation (Alzheimer's disease, primary liver cancer, progressive obstructive pulmonary disease) and one patient refused to participate. Although during a telephone interview with this last patient no swallowing and/or voice complaints were revealed, he was excluded because most multidimensional assessment data were missing. All patient data and reasons for exclusion at the various assessment points are provided in the consort flowchart (Fig. 1).

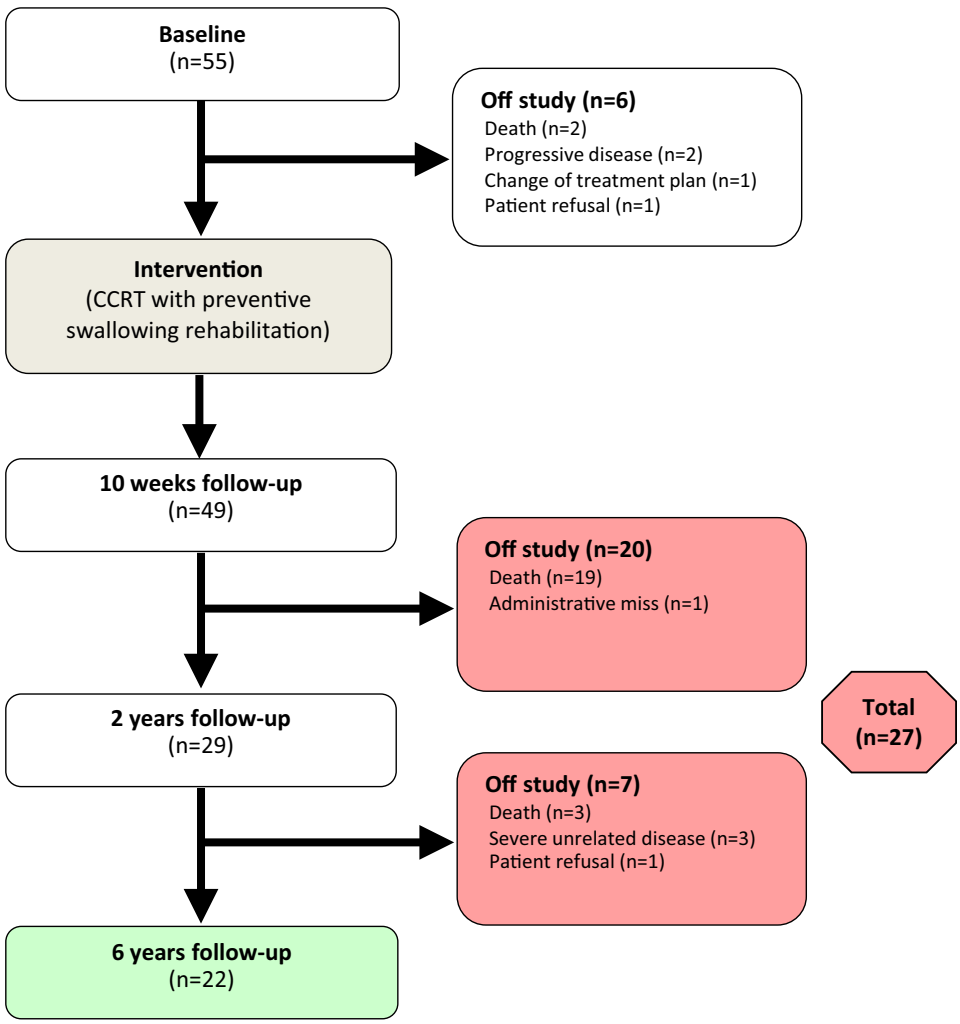

Fig. 1 Consort flowchart with patient data and reasons for exclusion at the various assessment points

Multidimensional assessment

As previously published [34, 44], assessment of functional (voice and swallowing) sequels was performed with multidimensional objective and subjective outcome measures. In short, the protocol included standard videofluoroscopy (VFS) to determine swallowing function, the Penetration and Aspiration Scale (PAS; score 1: material does not enter the airway, to 8: material enters the airway, passes below the vocal folds, and no effort is made to eject [46]), and an overall 'presence of residue' score (score 0: no residue, to score 3: residue above and below the vallecula, with minimal residue judged as normal). Maximum interincisor (mouth) opening (MIO) was measured in mm using the disposable TheraBite range of motion scale, and trismus was defined as a MIO of $\leq$35 mm [47]. Oral intake/nutritional status was assessed with the Functional Oral Intake Scale (FOIS; range from 1 to 7 with 1: nothing by mouth to 7: no oral restrictions), and with data on tube feeding dependency, weight change, and Body Mass Index (BMI). Pain was assessed with a visual analog scale (VAS) of 0–100 mm with zero being no pain and 100 being the worst possible pain (VAS; score 0–4 mm: no pain, to score 75–100: severe pain) [48].

Acoustic voice parameters (voicedness, fundamental frequency, harmonics-to-noise ratio, measures of spectral tilt, jitter and shimmer measures, and nasality) were derived from recordings in a quiet room of a standard Dutch text and sustained/a/. Acoustic analysis was performed with the program PRAAT (www.praat.org).

A study-specific questionnaire, in part based on the EORTC-HN and EORTC-C30, was used to evaluate patients' perception of swallowing function, mouth opening and voice quality, several QoL aspects, and compliance with the exercises [44]. Additionally, at the 6-year assessment point, the SWAL-QOL and the Voice Handicap Index (VHI) questionnaires were administered. The SWAL-QOL is one of the validated questionnaires for assessing patients' swallowing impairment (44-items that assess 10 QoL domains, each ranging from 0 to 100 with a higher score indicating more impairment) [49, 50]. The VHI is a validated 30-item questionnaire scored on a 0–4 point scale for measuring patients' subjective suffering caused by dysphonia, specified into three subscales (physical, functional, emotional) identified with ten items each. The total VHI score can range from 0 to 120 with a higher score corresponding to a higher degree of patient-reported vocal handicap (VHI score 0–30: minimal handicap; 31–60: moderate handicap; 60–120: significant and serious handicap) [51, 52]. At the start of the original RCT (2006) these questionnaires were not yet validated into Dutch, and thus these data are only available at the 6-year assessment point. All (other) outcome measures at 6 years post-treatment were compared with results at baseline and at 2 years post-treatment.

Statistical analysis

All data were collected and analyzed in a specially developed Statistical Package of Social Sciences database (SPSS, Inc, Chicago, Illinois; version 20.0). Concerning the functional outcome parameters, percentages of reported/measured disorders were calculated at each assessment point, comparable to the methods described by Logemann et al. [53]. McNemar's test with Bonferroni correction was used for pairwise comparisons among the various assessment points (baseline, 2 years- and 6 years post-treatment). Continuous variables (i.e., weight and MIO) were compared by means of paired t tests. For acoustic voice analysis, patients were divided into several subgroups according to tumor site. Independent sample t tests were used for comparisons between groups and paired t test were used for pairwise (subgroup) comparisons over time. For all analyses, a p value of $\leq$0.05 was considered to be statistically significant. Overall survival (OS) was calculated from randomization until death or last time of assessment. Survival curves were generated with the Kaplan–Meier method. The log-rank test was used to examine the difference in OS between subgroups.

Results

Patients' characteristics

At approximately 6 years (median follow-up 74 months, range 67–83 months) 22 patients (17 male and 5 female, mean age: 63 years; range 45–79 years) were disease free and evaluable. Three patients (all stage IV; 14 %), who had required a salvage neck dissection for residual regional disease, were kept in the analysis. Patients' and tumor characteristics of the total patient group that started and completed treatment ($n = 49$), of the evaluated patients ($n = 22$), and of those who were not evaluable ($n = 27$), are given in Table 1. Except for T-stage, there were no significant differences between the groups with respect to gender, mean age, tumor site, or general tumor stage (stage III or IV).

Swallowing function

Table 2 shows overall percentages of laryngeal penetration and/or aspiration, contrast residue, tube feeding, abnormal FOIS score, trismus, patients' perceived swallowing and mouth opening issues (e.g., xerostomia), pain (VAS), mean mouth opening (MIO) and mean weight. As can be seen,

Table 1 Clinical characteristics of patients at baseline ($n = 55$), patients at the 6-year assessment point ($n = 22$), and patients, who went off study ($n = 27$)

	Baseline	Patients who started treatment	
	Pre-treatment ($n = 55$)	6 years evaluated patients ($n = 22$)	Not evaluated patients ($n = 27$)
Gender			
Male (%)	44 (80)	19 (86)	22 (82)
Female (%)	11 (20)	3 (14)	5 (18)
Age at baseline (range)	58 (32–79)	57 (39–73)	56 (32–78)
Tumor site			
Nasopharynx[a] (%)	7 (13)	4 (18)	3 (11)
Oral cavity/ Oropharynx[a] (%)	29 (53)	10 (46)	14 (52)
Hypopharynx/ Larynx[b] (%)	19 (35)	8 (36)	10 (37)
NT group (%)	13 (24)	6 (27)	5 (19)
LHBT group (%)	42 (76)	16 (73)	22 (81)
Tumor stage			
Stage III (%)	17 (31)	10 (45)	6 (22)
Stage IV (%)	38 (69)	12 (55)	21 (78)
T-stage			
Tl (%)	8 (15)	5 (23)	3 (11)
T2 (%)	15 (27)	9 (41)	6 (33)
T3 (%)	21 (38)	7 (32)	12 (44)
T4 (%)	11 (20	1 (5)	6 (22)
N stage			
N0 (%)	6 (11)	2 (9)	2 (7)
Nl(%)	15 (27)	8 (36)	6 (22)
N2 (%)	28 (51)	8 (36)	18 (67)
N3 (%)	6 (11)	4 (18)	1 (4)
Exercise group			
Standard group (%)	28 (51)	10 (45)	12 (44)
Experimental group (%)	27 (49)	12 (55)	15 (56)

For acoustic analyses, tumor sites were grouped as *above hyoid bone*[a] and *below hyoid bone*[b], and according to velopharyngeal tumor extension (*NT group N*asopharyngeal and *T*onsil tumors, *LHBT group L*aryngeal, *H*ypopharyngeal, and *B*ase of *T*ongue tumors)

some functional problems were already present at baseline, related to tumor site and/or extension. Furthermore, Table 2 shows that many functional and QoL aspects had not significantly changed over the various assessment points, except increased xerostomia (baseline vs. 6 years; $p = 0.003$), ultimately reported by two-thirds of the patients. Despite the non-significant differences over time, some trends will be discussed.

Regarding swallowing function, the percentages of laryngeal penetration and/or aspiration and the frequency of more than normal residue above and below the hyoid bone on VFS ($n = 18$) remained more or less stable over time (this concerned mainly patients with a tumor located at the larynx or hypopharynx). None of the patients was dependent on tube feeding or on nutritional oral supplements at 6 years post-treatment. Regarding mouth opening, only one patient (5 %), who had been treated for a tumor located at the oropharynx (tonsillar carcinoma), showed trismus at the 6-year assessment point. Patients' perceived trismus was higher, and was reported by six patients (27 %), of whom four actually showed a measurable decreased MIO (mean decrease 8 mm; range 3–15 mm) compared to baseline values. Pain in the head and neck region was already present in 36 % of patients before treatment onset, decreased below baseline levels at 2 years post-treatment, and tended to increase again at 6 years post-treatment (32 %; $p = 0.06$). With respect to QoL issues related to swallowing function at 6 years post-treatment, xerostomia ($n = 15$; 68 %; especially in oropharyngeal cancer ($n = 9$) patients), and problems with swallowing solids (50 %) were most frequently reported.

Voice quality

Table 3 shows the subjective and objective voice parameters divided into subgroups according to tumor site above/below the hyoid bone (HB), and for the parameter nasality according to velopharyngeal tumor extension (nasopharyngeal and tonsil tumors) or not (laryngeal, hypopharyngeal, and base of tongue tumors). See Table 3 for the number of patients per subgroup. For subjective voice analysis ($n = 22$), mean VHI scores, as assessed at 6 years post-treatment, are shown. For acoustic voice analysis ($n = 19$), three patients were excluded due to missing data or poor quality of the voice recordings. For these parameters mean differences between measures at baseline and measures at 6 years are shown.

Regarding subjective voice outcomes at the 6-year assessment point, half of the patients ($n = 11$; 50 %) perceived their voice as different from baseline. The median total VHI score at 6 years post-treatment was 3 (mean = 12; range 0–91; $n = 22$). Patients with a tumor located below the HB ('below HB group') reported higher total VHI scores (mean = 21, median = 11, range 0–91), indicating more voice problems, in comparison with those with a tumor above the hyoid bone ('above HB group'; mean = 7, median = 1, range 0–47). In particular the physical and functional subscales of the VHI predicted the total VHI scores. Emotional voice problems were reported by seven patients, who all had high physical and functional VHI sub scores. Five were laryngeal cancer patients and

Table 2 Percentages of disorders and other measures observed at the various assessment points after concurrent chemoradiotherapy in 22 advanced head and neck cancer patients

Description of disorder ($n = 22$)	Pre-treatment Baseline *n* (%)	Post-treatment		McNemar's *p* value	
		2 years *n* (%)	6-years *n* (%)	Pre vs. 6 years	2 years 6 years
Videofluoroscopy ($n = 18$)					
Aspiration or penetration	3 (17)	3 (18)	4 (22)	1.0	1.0
Residue above and below hyoid	17 (94)	11 (65)	14 (78)	0.38	0.25
Feeding tube	0 (0)	0 (0)	0 (0)	×	×
Abnormal diet (FOIS score 1–6)	3 (14)	2 (9)	0 (0)	0.25	0.50
Pain (VAS)	8 (36)	2 (9)	7 (32)	1.0	0.06
Trismus	2 (9)	2 (9)	1 (5)	1.0	1.0
QOL aspect/issue					
Perceived decreased mouth opening	1 (5)	5 (23)	6 (27)	0.06	1.0
Xerostomia	4 (18)	13 (59)	15 (68)	**0.003**	0.63
Oral transport with solids	3 (14)	5 (23)	3 (14)	1.0	0.63
Oral transport with paste	2 (9)	1 (5)	1 (5)	1.0	1.0
Oral transport with liquids	0 (0)	1 (5)	1 (5)	1.0	1.0
Swallowing problems with solids	8 (36)	11 (50)	11 (50)	0.51	1.0
Swallowing problems with paste	2 (9)	1 (5)	2 (9)	1.0	1.0
Swallowing problems with liquids	1 (5)	0 (0)	2 (9)	1.0	0.50
Perceived different voice	8 (37)	14 (64)	11 (50)	1.0	0.51
Weight in kg (range)	82 (51–106)	80 (56–105)	81 (57–110)	0.61*	0.54*
Mouth opening in mm (range)	52 (26–69)	52 (20–70)	53 (21–70)	0.87*	0.40*

Bold value indicate statistical significance. Values marked by asterisks (*) mean compared mean *p* values; × means no statistical analyses possible. Videofluoroscopy records at 6 years post-treatment were available for 18 patients. If patients needed tube feeding, the QOL questions about oral transport and swallowing problems were not filled in

CCRT concurrent chemo-radiation therapy, *HNC* head and neck cancer, *FOIS* functional oral intake Scale, *QOL* quality of life

two were oropharyngeal cancer patients. The latter two received a high radiation dose (>55 Gy) to the larynx and both parotid glands.

For acoustic analysis of all voice parameters except voicedness and fundamental frequency (indicating pitch), one patient with a tumor below the HB was excluded because of the presence of a nasogastric feeding tube at baseline. It has to be noted that none of the patients suffered from a cold during voice recordings. Acoustic analysis of the read aloud text at baseline ($n = 19$) showed that patients in the 'below HB group' ($n = 7$) presented with significantly less voicedness than the patients in the 'above HB group' ($n = 12$; independent sample t test; $p = 0.011$). Over time, there was no improvement in both groups, and the difference was still significant at 6 years post-treatment ($p = 0.016$). There was also no significant improvement in the harmonics-to-noise ratio from baseline to 6 years post-treatment in both groups. Mean fundamental frequency during text aloud reading at 6 years post-treatment had not changed much for the 'above HB group', while it had significantly increased in the 'below HB group' ($p = 0.044$; see Fig. 2). Jitter measures had increased as well in the 'below HB group', while shimmer measures were stable over time. In contrast, in the 'above HB group' shimmer had improved while jitter was stable. Measures of spectral tilt (indicating vocal effort) on sustained/a/ at baseline showed more effort in the 'below HB group' ($p = 0.231$). At 6 years post-treatment, results had improved up to the level of the 'above HB group' (see Fig. 3). Velopharyngeal function was analyzed by nasality (antiformants) in sustained/a/. The patients were divided into subgroups according to velopharyngeal tumor extension ('NT group': *N*asopharyngeal and *T*onsil tumors; $n = 6$) or not ('LHBT group': *L*aryngeal, *H*ypopharyngeal, and Base of *T*ongue tumors; $n = 12$). While the 'NT group' showed improvements after 2 years compared to baseline, at 6 years post-treatment the measures had worsened again. Also in the 'LHBT group' there was a trend that the measures had worsened compared to baseline values (paired t test $p = 0.087$).

General treatment outcomes

Beyond 6 years of treatment, 24 of the included 55 patients (44 %) had died; 14 patients had died of progressive (recurrent or residual) disease, two patients had died of a

Table 3 Subjective and objective voice parameters divided according to tumor site

	Above hyoid bone group			Below hyoid bone group			Total		
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Voice Handicap Index (VHI) score	14	6.86	14.13	8	21.00	29.80	22	12.00	21.64
VHI physical domain	14	2.86	5.91	8	10.13	10.11	22	5.50	8.27
VHI functional domain	14	2.71	5.18	8	5.75	8.97	22	3.82	7.46
VHI emotional domain	14	1.29	3.12	8	5.13	11.75	22	2.68	7.46
Voicedness/text/	12	−1.50	8.19	7	0.14	7.38	19	−0.89	7.73
Fundamental frequency/text/	12	−2.92	23.20	7	−12.71	13.24	19	−6.53	20.27
Harmonics-to-noise ratio/a/	12	−1.81	4.72	6	−0.52	3.55	18	−1.38	4.30
Measures of spectral tilt/a/	12	−2.91	4.63	6	−4.88	7.91	18	−3.57	5.76
Jitter/a/	12	0.00	0.65	6	−0.21	0.47	18	−0.07	0.59
Shimmer/a/	12	2.60	3.28	6	−0.37	4.54	18	1.61	3.88

	NT group			LHTB group			Total		
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Nasality/a/	6	−3.59	6.61	12	0.72	6.04	18	−2.15	6.59

For subjective voice analysis ($n = 22$), mean Voice Handicap Index (VHI) scores, as assessed at 6 years post-treatment, are shown. For acoustic voice analysis ($n = 19$), mean differences between measures at baseline and measures at 6 years are shown. For all acoustic voice parameters except voicedness and fundamental frequency, one patient with a tumor below the hyoid bone was excluded because of the presence of a nasogastric feeding tube at baseline

Above hyoid bone group Oral cavity, Oropharyngeal (tonsil and base of tongue), and Nasopharyngeal tumors, *Below hyoid bone group* Laryngeal and Hypopharyngeal tumors, *NT group* *N*asopharyngeal and *T*onsil tumors, *LHBT group* *L*aryngeal, *H*ypopharyngeal, and *B*ase of *T*ongue tumors

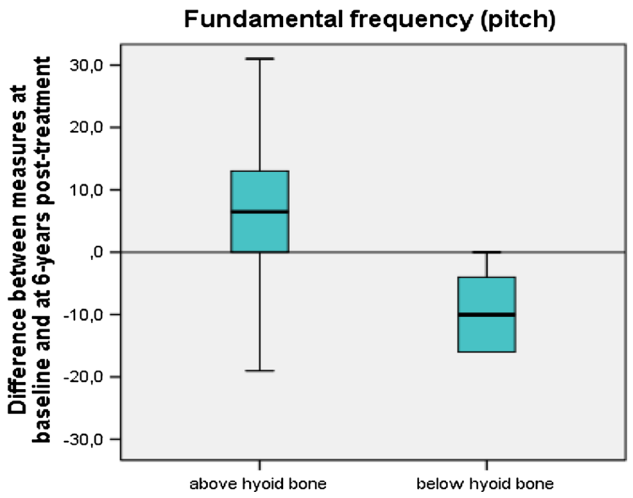

Fig. 2 Change in fundamental frequency ("pitch") between measures at baseline and at 6 years post-treatment among patients with a tumor above the hyoid bone ($n = 12$) and below the hyoid bone ($n = 7$). Negative values mean increased pitch between the two assessment points

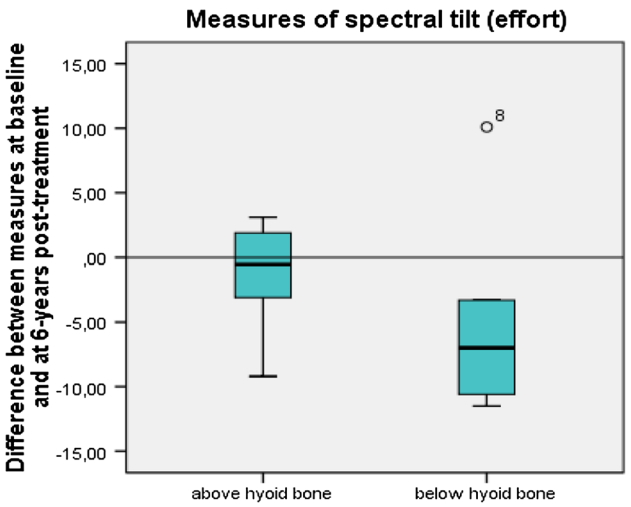

Fig. 3 Change in measures of spectral tilt ("vocal effort") between baseline and 6 years post-treatment among patients with a tumor above the hyoid bone ($n = 12$) and below the hyoid bone ($n = 6$). Negative values show a decrease in vocal effort between the two assessment points

second primary malignancy (lung and liver) and eight patients had died due to other/unknown causes. The 6-year-overall survival (OS) rate, based on the original cohort of 55 patients, was 60 %. Both tumor stage and site (stage IV, oral cavity) were found to be associated with poorer OS in this patient cohort. Patients with a tumor located at the nasopharynx ($n = 7$) showed the best OS. See Fig. 4 for the Kaplan–Meier curves for OS per tumor stage.

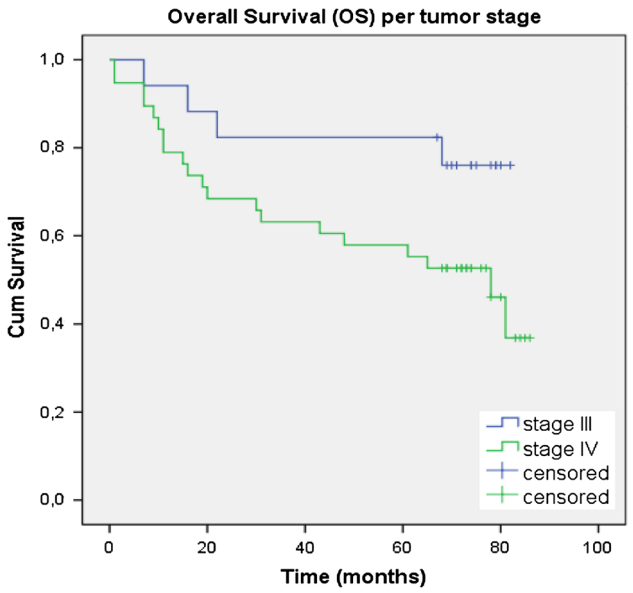

Fig. 4 Kaplan–Meier curve for overall survival (OS) per tumor stage with poorer OS ($p = 0.067$) for stage IV tumors compared to stage III tumors

Discussion

This prospective clinical study on swallowing function and voice quality in advanced head and neck cancer (HNC) patients treated with concurrent chemoradiotherapy (CCRT) and preventive swallowing exercises shows that functional swallowing and voice problems at 6 years post-treatment are minimal. Moreover, no significant changes since the one-year (voice quality [34])- or 2-year (swallowing function [25])-assessment points are found.

Swallowing function

In the earlier reports on this CCRT-preventive swallowing rehabilitation trial, outcomes were compared with an in-house preceding RCT on CCRT with a similar (IMRT) therapy protocol, except for the application of this preventive swallowing rehabilitation protocol. Since the 5-year results of this latter trial are published as well [54], and data from prospective studies with longer follow-up after preventive swallowing rehabilitation still are scarce [19], it is again possible and interesting to also compare the more long-term results of both trials. Regarding swallowing function and oral intake, in that earlier study it was found that 7/71 patients (10 %) still required tube feeding at 5 years post-treatment, whereas in the present study all patients were able to consume a normal oral diet at the 6-year assessment point. In the preceding CCRT study, no objective evaluation of swallowing function was performed, which precludes comparison of those data available for the present study. Comparison to some extent is possible with the study of Hutcheson et al. [33], which evaluated late dysphagia (dysphagic patients with a median of 9 years post-treatment), and included videofluoroscopic studies. Pharyngeal residue and aspiration was found in all patients, with silent aspiration occurring in 23/28 patients (82 %). Six patients (21 %) were feeding tube dependent and 11 patients (38 %) had developed trismus. However, only symptomatic dysphagic patients were evaluated in that study, precluding estimate of the prevalence of late dysphagia, and in depths comparison with our findings.

It is not unlikely that the favorable swallowing outcomes in the present study can be attributed to the preventive and continued post-treatment rehabilitation programs, which were applied in this patient cohort. Preventive rehabilitation programs have been associated with better post-treatment swallowing outcomes before [20–26], especially on the short-term [19], and probably, the exercises applied are associated with better long-term results as well.

Patients' perceived functional changes correlated only weakly with objective outcome measures. Regarding swallowing function, only one of the four patients who showed laryngeal penetration or aspiration on VFS, actually reported of swallowing problems. With regards to trismus, there was only one patient (5 %) who actually fulfilled the criterion for an objective trismus (MIO $\leq$ 35 mm). Interestingly, however, patients' perceived trismus was higher ($n = 6$, including the objective trismus patient; 27 %), and in four of these six patients the MIO did show a measurable decrease (mean 8 mm) compared to baseline values. Therefore, clinical outcome measures should always be combined with patients' views, to gain best insight in the extent of the functional problems.

Voice quality

Since combined CCRT regimens can have adverse effects on voice quality as well, assessment of functional sequels of CCRT should include patients' voice quality, e.g., by calculating means of acoustic parameters at the various assessment points. In the present cohort, due to positive lymph nodes, the vast majority of patients (20/22) received a radiation dose of 43.5 Gy and higher to the larynx, which has been described in the literature as cutoff value for developing voice problems or chronic edema [4, 5]. Voice problems can also occur due to changes in saliva production and lubrication, mainly as a result of radiation dose to the parotid gland and the laryngeal mucosa, which can lead to insufficient lubrication/dryness of the vocal folds [37, 55]. Hence, the fact that generally all patients with a tumor located at the larynx or hypopharynx (still) demonstrated less voicedness and increased fundamental frequency at voice recordings at 6 years post-treatment is

understandable. Interestingly, although this concerned only six patients, patients with a tumor located at the tonsil or nasopharynx, who had shown improvements in nasality at the 2-year assessment point, showed increased nasality again at the 6-year assessment point. Previously, only few studies with adequate pre-treatment data prospectively investigated effects of CCRT on voice quality, and the available studies often used different diagnostic tests [9–11, 34, 36]. Longest follow-up was a year in all, except for the study of Vainshtein et al. [6] that evaluated voice changes up to 2 years following CCRT. However, only patient-reported voice quality was assessed in that study, while especially acoustic voice parameters at long-term follow-up would be informative, since changes in voice quality (i.e., more nasality) after 6 years of follow-up are demonstrable in our study.

Subjective voice complaints were evaluated in the present patient cohort with some study-specific questions ("do you perceive your voice as different from baseline"?) and with (sub) total VHI scores. Previously, subjective voice outcomes showed that 70 % of patients reported their voice as different from baseline to one year post-treatment [56]. Besides, most of the laryngeal and hypopharyngeal cancer patients already presented with voice problems at the time of diagnosis. At 6 years post-treatment, (still) half of the patients (50 %) perceived their voice as different from baseline. Patients with a functional and/or physical voice disability (based on VHI sub scores [51]) reported of problems such as increased vocal effort, breathiness, and hoarseness. To date, there are little studies that evaluated VHI scores after CCRT treatment for HNC, especially at long term. In recent studies that evaluated voice quality, results showed decreases in voice quality following CCRT [6, 40], with an impact on QoL and emotional distress [42]. Though almost the whole VHI range (0–91) was covered in our patient population (with various tumor sites included) at 6 years post-treatment, the median total VHI score was only three. Apparently, the subjectively perceived and acoustically measured changes in voice quality were not considered a handicap for the vast majority of our patients.

Limitations

In prospective trials, patients are lost to follow-up because of death, or of progressive, residual or recurrent disease, which always forms a limitation in long-term evaluation of functional treatment results. Moreover, there might be a survival bias towards patients with good functional outcomes. Longer term severe unrelated disease and patient refusal are further decreasing the sample on which conclusions have to be based upon. And obviously, as can be seen in Table 1, more stage III than stage IV patients are surviving/evaluable (originally 33–66, and at 6 years almost 50–50). As a result, some selection bias cannot be excluded in the present study, which might as well in part explain the limited functional problems in the analyzed patient cohort. However, except for initial T-stage, the patient group at 6 years post-treatment ($n = 22$) still is comparable to the group at baseline ($n = 49$) concerning most patient and tumor characteristics (age, gender, tumor site and stage, etc.). Also the patients who went "off-study" after initial treatment ($n = 27$) did not differ significantly on most of these parameters from the currently analyzed patients ($n = 22$).

Conclusion

This is one of the first studies investigating CCRT-induced effects on swallowing function and voice quality in HNC patients 6 years after treatment. Overall, functional problems at 6 years post-treatment are minimal in this patient cohort, possibly due to the preventive and continued post-treatment swallowing rehabilitation programs applied.

Acknowledgments Harm van Tinteren, certified statistician at the Netherlands Cancer Institute is greatly acknowledged for his support and advice in the statistical analysis. This study was made possible by grants provided by "Stichting de Hoop" and the Verwelius Foundation.

References

1. Pignon JP, le Maitre A, Maillard E, Bourhis J (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol J Eur Soc Ther Radiol Oncol 92(1):4–14
2. Hutcheson KA, Lewin JS (2012) Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. Curr Oncol Rep 14(2):158–165
3. Metreau A, Louvel G, Godey B, Le Clech G, Jegoux F (2014) Long-term functional and quality of life evaluation after treatment for advanced pharyngolaryngeal carcinoma. Head Neck 36(11):1604–1610
4. Sanguineti G, Adapala P, Endres EJ, Brack C, Fiorino C, Sormani MP, Parker B (2007) Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys 68(3):741–749
5. Nguyen NP, Abraham D, Desai A, Betz M, Davis R, Sroka T, Chi A, Gelumbauskas S, Ceizyk M, Smith-Raymond L, Stevie M, Jang S, Hamilton R, Vinh-Hung V (2011) Impact of image-guided radiotherapy to reduce laryngeal edema following treatment for non-laryngeal and non-hypopharyngeal head and neck cancers. Oral Oncol 47(9):900–904
6. Vainshtein JM, Griffith KA, Feng FY, Vineberg KA, Chepeha DB, Eisbruch A (2014) Patient-reported voice and speech outcomes after whole-neck intensity modulated radiation therapy and chemotherapy for oropharyngeal cancer: prospective longitudinal study. Int J Radiat Oncol Biol Phys 89(5):973–980
7. Fung K, Yoo J, Leeper HA, Bogue B, Hawkins S, Hammond JA, Gilchrist JA, Venkatesan VM (2001) Effects of head and neck radiation therapy on vocal function. J Otolaryngol 30(3):133–139

8. Starmer HM, Tippett DC, Webster KT (2008) Effects of laryngeal cancer on voice and swallowing. Otolaryngol Clin North Am 41(4):793–818
9. Bibby JR, Cotton SM, Perry A, Corry JF (2008) Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck 30(5):600–610
10. Kazi R, Venkitaraman R, Johnson C, Prasad V, Clarke P, Newbold K, Rhys-Evans P, Nutting C, Harrington K (2008) Prospective, longitudinal electroglottographic study of voice recovery following accelerated hypofractionated radiotherapy for T1/T2 larynx cancer. Radiother Oncol 87(2):230–236
11. Agarwal JP, Baccher GK, Waghmare CM, Mallick I, Ghosh-Laskar S, Budrukkar A, Pai P, Chaturvedi P, D'Cruz A, Shrivastava SK, Dinshaw KA (2009) Factors affecting the quality of voice in the early glottic cancer treated with radiotherapy. Radiother Oncol 90(2):177–182
12. Jacobi I, van der Molen L, Huiskens H, van Rossum MA, Hilgers FJ (2010) Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol 267(10):1495–1505
13. Lazarus CL, Husaini H, Hu K, Culliney B, Li Z, Urken M, Jacobson A, Persky M, Tran T, Concert C, Palacios D, Metcalfe-Klaw R, Kumar M, Bennett B, Harrison L (2014) Functional outcomes and quality of life after chemoradiotherapy: baseline and 3 and 6 months post-treatment. Dysphagia 29(3):365–375
14. Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, Moyer JS, Prince ME, Carey TE, Wolf GT, Bradford CR, Chepeha DB, Eisbruch A (2010) Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol 28(16):2732–2738
15. Mowry SE, Tang C, Sadeghi A, Wang MB (2010) Standard chemoradiation versus intensity-modulated chemoradiation: a quality of life assessment in oropharyngeal cancer patients. Eur Arch Otorhinolaryngol 267(7):1111–1116
16. Roe JW, Carding PN, Dwivedi RC, Kazi RA, Rhys-Evans PH, Harrington KJ, Nutting CM (2010) Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head and neck cancer—a systematic review. Oral Oncol 46(10):727–733
17. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, Worden FP, Bradford CR, Prince ME, Moyer JS, Wolf GT, Chepeha DB, Ten Haken RK (2011) Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys 81(3):93–99
18. Peponi E, Glanzmann C, Willi B, Huber G, Studer G (2011) Dysphagia in head and neck cancer patients following intensity modulated radiotherapy (IMRT). Radiat Oncol 6:1
19. Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ (2014) Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care 8(2):152–163
20. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, Magnuson JS (2006) Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope 116(6):883–886
21. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS (2008) Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope 118(1):39–43
22. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R (2012) "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys 83(1):210–219
23. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, Forsythe K, Genden EM (2012) Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg 138(4):376–382
24. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ (2011) A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia 26(2):155–170
25. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ (2013) Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol 271(5):1257–1270
26. Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, Lewin J (2013) Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg 139(11):1127–1134
27. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, Newman K, Purdy JA, Vijayakumar S (2010) Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 78(4):1026–1032
28. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM (2012) Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia 27(2):251–259
29. Eisbruch A, Lyden T, Bradford CR, Dawson LA, Haxer MJ, Miller AE, Teknos TN, Chepeha DB, Hogikyan ND, Terrell JE, Wolf GT (2002) Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 53(1):23–28
30. Goguen LA, Posner MR, Norris CM, Tishler RB, Wirth LJ, Annino DJ, Gagne A, Sullivan CA, Sammartino DE, Haddad RI (2006) Dysphagia after sequential chemoradiation therapy for advanced head and neck cancer. Otolaryngol Head Neck Surg 134(6):916–922
31. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, Dutta S, Midyett FA, Barloon J, Sallah S (2004) Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol 15(3):383–388
32. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, Nguyen LM, Rose S, Dutta S, Sallah S (2006) Evolution of chronic dysphagia following treatment for head and neck cancer. Oral Oncol 42(4):374–380
33. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, Holsinger FC (2012) Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer 118(23):5793–5799
34. L van der Molen, I Jacobi, MA van Rossum, FJ Hilgers (2010) Pre- and short-term Posttreatment vocal functioning in patients with advanced head and neck cancer treated with concomitant chemoradiotherapy. Interspeech 2582–2585
35. Adams G, Burnett R, Mills E, Penniment M (2013) Objective and subjective changes in voice quality after radiotherapy for early (T1 or T2, N0) laryngeal cancer: a pilot prospective cohort study. Head Neck 35(3):376–380
36. Jacobi I, van Rossum MA, van der Molen L, Hilgers FJ, van den Brekel MW (2013) Acoustic analysis of changes in articulation proficiency in patients with advanced head and neck cancer treated with chemoradiotherapy. Ann Otol Rhinol Laryngol 122(12):754–762
37. Lazarus CL (2009) Effects of chemoradiotherapy on voice and swallowing. Curr Opin Otolaryngol Head Neck Surg 17(3):172–178

38. Oridate N, Homma A, Suzuki S, Nakamaru Y, Suzuki F, Hatakeyama H, Taki S, Sakashita T, Nishizawa N, Furuta Y, Fukuda S (2009) Voice-related quality of life after treatment of laryngeal cancer. Arch Otolaryngol Head Neck Surg 135(4):363–368
39. Thomas L, Jones TM, Tandon S, Carding P, Lowe D, Rogers S (2009) Speech and voice outcomes in oropharyngeal cancer and evaluation of the University of Washington Quality of Life speech domain. Clin Otolaryngol 34(1):34–42
40. Keereweer S, Kerrebijn JD, Al-Mamgani A, Sewnaik A, Baatenburgde Jong RJ, van Meerten E (2012) Chemoradiation for advanced hypopharyngeal carcinoma: a retrospective study on efficacy, morbidity and quality of life. Eur Arch Otorhinolaryngol 269(3):939–946
41. Myers C, Kerr P, Cooke A, Bammeke F, Butler J, Lambert P (2012) Functional outcomes after treatment of advanced oropharyngeal carcinoma with radiation or chemoradiation. J Otolaryngol Head Neck Surg 41(2):108–118
42. Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, Leemans CR (2014) Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol 50(8):759–764
43. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ (2009) Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. Eur Arch Otorhinolaryngol 266(11):1687–1698
44. van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ (2009) Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord 9:10
45. van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, Hilgers FJ (2013) Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol 106(3):364–369
46. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL (1996) A penetration-aspiration scale. Dysphagia 11(2):93–98
47. Dijkstra PU, Huisman PM, Roodenburg JL (2006) Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg 35(4):337–342
48. Jensen MP, Chen C, Brugger AM (2003) Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 4(7):407–414
49. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR (2009) The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. Oral Oncol 45(8):67–71
50. Lemmens J, Bours GJ, Limburg M, Beurskens AJ (2013) The feasibility and test-retest reliability of the Dutch Swal-Qol adapted interview version for dysphagic patients with communicative and/or cognitive problems. Qual Life Res 22(4):891–895
51. Jonhson A, Jacobsen B, Grywalski C, Silbergleit A, Jacobsen G, Benninger M (1997) The voice handicap index (VHI): development and validation. Am J Speech Lang Pathol 6(3):66–70
52. Verdonck-de Leeuw IM, Kuik DJ, De Bodt M, Guimaraes I, Holmberg EB, Nawka T, Rosen CA, Schindler A, Whurr R, Woisard V (2008) Validation of the voice handicap index by assessing equivalence of European translations. Folia Phoniatr Logop 60(4):173–178
53. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Gaziano J, Stachowiak L, Newman L, MacCracken E, Santa D, Mittal B (2008) Swallowing disorders in the first year after radiation and chemoradiation. Head Neck 30(2):148–158
54. Ackerstaff AH, Rasch CR, Balm AJ, de Boer JP, Wiggenraad R, Rietveld DH, Gregor RT, Kroger R, Hauptmann M, Vincent A, Hilgers FJ (2012) Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck 34(7):974–980
55. Hamdan AL, Geara F, Rameh C, Husseini ST, Eid T, Fuleihan N (2009) Vocal changes following radiotherapy to the head and neck for non-laryngeal tumors. Eur Arch Otorhinolaryngol 266(9):1435–1439
56. van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, Hilgers FJ (2012) Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice Off J Voice Found 26(5):625–633