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Long-term swallowing, trismus, and speech outcomes after combined chemoradiotherapy and preventive rehabilitation for head and neck cancer; 10-year plus update

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Abstract

Background: The objective of this study was to explore the 10-year plus outcomes of Intensity Modulated Radiotherapy with concomitant chemotherapy (CRT) combined with preventive swallowing rehabilitation (CRT+) for head and neck cancer (HNC).

Methods: Subjective and objective swallowing, trismus, and speech related outcomes were assessed at 10-year plus after CRT+. Outcomes were compared to previously published 6-year results of the same cohort.

Results: Fourteen of the 22 patients at 6-year follow-up were evaluable. Although objective swallowing-related outcomes showed no deterioration (eg, no feeding tube dependency and no pneumonia), swallowing-related quality of life slightly deteriorated over time. No patients had or perceived trismus. Voice and speech questionnaires showed little problems in daily life. Overall quality of life (QOL) was good.

Conclusions: After CRT with preventive rehabilitation exercises for advanced HNC, swallowing, trismus, and speech related outcomes moderately deteriorated from 6 to 10 years, with an on average good overall QOL after.

KEYWORDS

chemoradiotherapy, dysphagia, head and neck cancer, preventive rehabilitation, speech, trismus

1 | INTRODUCTION

Advanced stage head and neck cancer (HNC) is commonly treated with chemoradiotherapy (CRT).¹ Although CRT is an organ-preserving treatment modality, it is associated with substantial toxicities.² Despite efforts to reduce radiotherapy dose on swallowing-related structures (ie, with

intensity-modulated radiotherapy [IMRT]), toxicities such as dysphagia are still a serious burden for survivors of advanced HNC.³

Currently, strategies to preserve or strengthen swallowing musculature before, during, or after treatment are making their way into regular care. Although the evidence is limited, some studies with good patient compliance have suggested benefit of preventive rehabilitation.⁴⁻¹⁶ At our institute, a randomized controlled trial (RCT) was

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performed, comparing preventive rehabilitation with and without the TheraBite Jaw Motion Rehabilitation System (Atos Medical, Sweden, Malmö).⁶ Functional outcomes and quality of life after treatment up until 6-year follow-up were comparable in both groups, besides less trismus in the TheraBite arm.^{6,10,17} A cost-effectiveness study using data of this study suggested that preventive rehabilitation, with or without TheraBite, is more cost effective than usual care.¹⁸

Due to increased survival of patients treated for HNC because of changing etiology and continuously improving treatment strategies, knowledge on long-term functional outcomes is essential.¹⁹ Functional outcomes of our preventive rehabilitation cohort have been described up until 6 years post-treatment.^{6,10,17} Up until that time, functional outcomes were comparable between the two exercise groups. In both groups, functional impairments were limited and more or less stable with no patients being feeding tube dependent at both 2- and 6-year follow-up. At 2- and 6-year follow-up 3 (10%) and 0 (0%) patients had a modified diet, respectively, and 2 (7%) and 1 (5%) patient(s) had trismus. Data from earlier studies on toxicities beyond this period have suggested that functional impairment after (C)RT may develop or worsen during the years after the end of treatment, possibly due to continued fibrosis of swallowing structures.²⁰⁻²² Since preventive rehabilitation strategies are now applied more broadly, long-term outcomes may have improved, which could be relevant to medical decision-making. Data on long-term functional outcomes after CRT with preventive swallowing rehabilitation are however currently lacking.

The objective of this study was to explore the functional outcomes and quality of life of the patients now more than 10 years after CRT with preventive rehabilitation (with and without TheraBite), whose 1-, 2- and 6-year data were assessed earlier.¹⁷ Functional outcomes at 10 year-plus follow-up will be compared to those at 6-year follow-up.

2 | METHODS

2.1 | Approval and consent

This study was approved by the medical research ethics committee of the Netherlands Cancer Institute (METC17.1906/N17SSF). Written informed consent was obtained from all patients.

2.2 | Patient selection

All evaluable, disease-free patients who participated in the previously published RCT comparing preventive rehabilitation

with and without the TheraBite Jaw Motion Rehabilitation System during CRT for HNC in the Netherlands Cancer Institute (NKI-AVL) were included in the analysis.^{6,10,17,23} Initially, 55 patients treated with cisplatin-based CRT between September 2006 and April 2008 with curative intent for stage III to IV cancer of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx were included. All patients received 70 Gy of IMRT in 35 fractions over 7 weeks with concomitant cisplatin (100 mg/m²) on days 1, 22, and 43. All 55 included patients received preventive exercises (randomized for exercises with or without the TheraBite) which included jaw range of motion and swallowing exercises. They were instructed to perform the exercises daily from the start of treatment up until 1 year afterwards, as described by van der Molen et al.⁶ In summary, the experimental exercises consisted of a stretch exercise (ie, passive and slow opening of the mouth using the TheraBite) and a strengthening exercise (ie, swallow with tongue elevated to the palate at 50% of the maximal mouth opening using the TheraBite). The standard rehabilitation consisted of five range of motion exercises and three strengthening exercises (ie, Masako maneuver, effortful swallow and super-supraglottic swallow).

2.3 | Data collection

The selection of outcomes measures collected in the present study were based on the data collected 6 years after CRT.¹⁷ Baseline characteristics included gender, age at start CRT, tumor site, T and N classification (American Joint Committee on Cancer [AJCC] seventh edition), AJCC stage, and preventive rehabilitation type (with or without TheraBite).

2.4 | Swallowing-related outcomes

The following swallowing outcomes and adverse events that might be related to swallowing impairment were assessed: history of pneumonia since 6-year follow-up (according to patient and notes in medical chart), feeding tube dependency, and body weight. Videofluoroscopy was recorded in an upright position in lateral view with 25 frames per second. The subject was asked to swallow 3 and 10 cc thin liquid, 5 cc thick liquid, and a piece of gingerbread coated in Omnipaque consecutively from a spoon (Omnipaque contrast agent, GE Healthcare, Chicago, Illinois). The validated Dynamic Imaging Grade for Toxicity (DIGEST) grading system was used to rate pharyngeal swallowing safety (penetration/aspiration) and efficiency (residue) (see Appendix 1).^{24,25} Videofluoroscopy studies were scored blinded for follow-up moment. The safety

grade is assessed by means of the Penetration Aspiration Scale over all bolus trials.²⁶ Efficiency is assessed by estimating the maximum percentage of pharyngeal residue over all bolus trials (either <10%, 10%-49%, 50%-90%, or >90%). The DIGEST grade combines both safety and efficiency in a five-point ordinal scale ranging from grade 0 (no pharyngeal dysphagia) to grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life threatening). All video-fluoroscopy studies were assessed by two of the researchers who came to a consensus afterward. Oral diet was assessed by means of the Functional Oral Intake Scale (FOIS), which reflects the oral intake on a seven-point ordinal scale with scores below 7 indicating a modified diet.²⁷ A visual analog scale (VAS) of 0 to 100 mm was used to assess pain with scores greater than 4 mm indicating pain.²⁸

Also, subjective swallowing-related outcomes were assessed by means of a study-specific questionnaire as described earlier.²⁹ The questionnaire included questions on whether the patient perceived xerostomia, difficulty swallowing and masticating, and problems with oral transport or swallowing of solids, thick liquids and/or thin liquids (outcome was dichotomized into *no* meaning not at all, and *yes* meaning a little, quite a bit or very much). Also, patients were asked whether they have been continuing performing the rehabilitation exercises after the 1-year training period post CRT.

2.5 | Trismus-related outcomes

To assess trismus, we measured the maximal inter-incisal opening (MIO) by means of the TheraBite Jaw Range of Motion Scale (Atos Medical AB, Malmö, Sweden), and used a mouth opening of 35 mm or smaller as a criterion for trismus.³⁰ The MIO was measured by two different raters at timepoints, which might cause inter-rater variability. However, the inter-rater reliability of mouth opening measurement is very high (intraclass correlation coefficient of 0.98).³¹ To increase reliability of the measurements in our study, two measurements were taken at each timepoint with the highest value as maximal MIO. Also, subjects were asked if they perceived their mouth opening as deteriorated.

2.6 | Voice- and speech-related outcomes

Speech recordings consisted of an excerpt from a standard, balanced 189 word long Dutch text called “De vijvervrouw” and a sustained /a/. The recordings were automatically analyzed by the program Automatic Speech analysis In Speech Therapy for Oncology (ASISTO).^{32,33} This program determined the intelligibility based on Alignment-free

phonological and phonemic features (ALF-PPFs) with scores ranging from 0% to 100%. Voice quality was determined with the Acoustic Voice Quality Index (AVQI, version 2.03) (1 [normal]-8 [least normal]; a value <2.92 reflects normal voice quality) using 4 seconds of the running speech and 3 seconds of the sustained /a/.^{34,35} Speech recordings from the 6-year follow-up were unavailable for re-evaluation. Therefore, results from the analyses performed for the earlier published paper by Kraaijenga et al. on voice quality at 6-year follow-up were reported, which were analyzed using an earlier version of the ASISTO software.

As subjective outcome, patients were asked whether they perceived their voice as different.

2.7 | Quality of life-related outcomes

Symptom-related quality of life questionnaires were used. The Dutch version of the Swallowing Quality-of-Life questionnaire (SWAL-QOL), a validated 44-item questionnaire on dysphagia and its influence on daily life, was assessed. All scores range from 0 to 100 with higher scores indicating more dysphagia-related problems, and scores ≥14 points indicating swallowing problems in daily life.³⁶⁻³⁸ Subjective speech and voice function were assessed by means of the validated Dutch versions of the Voice Handicap Index (VHI) and Speech Handicap Index (SHI), respectively. These are both 30-item voice/speech-related quality of life questionnaires with higher scores indicating more speech/voice-related problems.³⁹⁻⁴² A VHI score of 15 or higher, and a SHI score of 6 or higher indicate voice, respectively, speech problems in daily life.^{38,43}

Also, overall quality of life was assessed by means of the EQ-5D-5L. The EQ-5D-5L includes the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of severity ranging from no to extreme burden. We dichotomized outcomes in to any burden (slight, moderate, severe, unable to perform) and no burden. The five dimensions are completed by the EQ-VAS, which records the patient's self-rated health on a visual analogue scale ranging from worst (0) to best (100) health.

2.8 | Statistical analysis

Analyses were performed using IBM SPSS Statistics 23.0 and R 3.6.2. Baseline characteristics and outcomes at both 6 and 10 years after treatment were presented using descriptive statistics. Medians and ranges were used for numerical and ordinal variables. For proportions, the Wilson score 95% confidence intervals (CIs) were

calculated. For medians, bootstrapping was used to estimate 95% CIs. For comparison, outcomes at 6-year follow-up are described only of the 14 patients evaluable at 10-year plus follow-up. With the small sample size of this study, which was inevitable for the given patient population, only very large changes will be statistically significant using the traditional cut-off of $P = .05$ for statistical significance. Also, absence of statistically significant changes cannot be interpreted as evidence for no change. We therefore consider these results to be descriptive, rather than inferential, and accordingly we refrained from hypothesis testing. Instead, we interpret the measurements based on their clinical meaning for the individuals in the sample.

3 | RESULTS

3.1 | Baseline characteristics

Of the 22 patients evaluable 6 years after CRT with preventive rehabilitation,¹⁷ 14 patients were evaluable for participation at 10-year plus (see Figure 1 for the study flow chart). Of the eight unevaluable patients, three refused participation (one had lost his wife recently and two had other priorities). One patient could not be evaluated because she had a second primary esophageal carcinoma. Four patients had died in the meantime. Three died of unrelated causes (one died from injuries after a fall off stairs, one from heart failure, and one from a status epilepticus caused by a glioblastoma). The fourth patient died at home at the age of 76 from respiratory insufficiency caused by a pneumonia of unknown etiology. The median follow-up of the 14 evaluable patients was 128 months (range 120-139 months) after the start of CRT. None of the patients continued with the (preventive) exercises after 1-year post CRT. Baseline characteristics are presented in Table 1.

3.2 | Swallowing-related outcomes

Swallowing-related outcomes at 6- and 10-year plus follow-up, respectively, are presented in Table 2. Pharyngeal dysphagia based on DIGEST grades increased in 5 out of 10 patients with videofluoroscopy available, due to a decreased efficiency ($n = 3$), decreased safety ($n = 1$), or both ($n = 1$). Similar to the last follow-up, none of the currently evaluable patients were feeding tube dependent, or required a modified diet (FOIS <7). None of the patients had had a pneumonia since last follow-up, but, as mentioned above, one of the currently non-evaluable patients, a 76-year old male, had died of pneumonia of unknown etiology after the last follow-up at 6 years, in

which case aspiration as etiology obviously cannot be excluded. This patient had no penetration or aspiration on videofluoroscopy at 6-year follow-up. The number of patients who perceived difficulty with oral transport of solids increased between 6- and 10-year plus follow-up from 2 to 7 patients. For thick liquids, this increased from 1 to 3 patients, and for thin liquids from 0 to 2 patients.

3.3 | Trismus-related outcomes

Trismus-related outcomes are presented in Table 3. Median mouth opening deteriorated from 51 (range 36-70) to 45 (range 36-86), but no patients had a mouth opening at or below the cut-off value of 35 mm indicating trismus.³⁰ Also, none of the patients at 10-year plus follow-up perceived their mouth opening as deteriorated, including the four patients who had perceived their mouth opening as deteriorated at 6-year follow-up.

3.4 | Voice- and speech-related outcomes

Voice- and speech-related outcomes are presented in Table 4. The objective voice quality (based on the AVQI) worsened from 4.7 (range 3.7-6.1) to 3.9 (1.6-8.0). The objective intelligibility (based on the ALF-PPFs) deteriorated slightly between 6- and 10-year plus follow-up from 85 (range 67-92) to 75 (69-87). Less patients perceived their voice as different at 10-year plus follow-up (50%) compared to 6-year follow-up (57%).

3.5 | Quality of life-related outcomes

See Table 5 for all quality of life-related outcomes. Scores increased moderately on all of the Dutch SWAL-QOL subscales, except for "food selection" and "fear of eating", indicating a deteriorated swallowing-related quality of life. Also, the median total SWAL-QOL score deteriorated from 12 (range 0-58) to 22 (range 0-41), which is above the cut-off value of 14, indicating swallowing problems in daily life. At 6-year follow-up, 5 of the 13 patients (39%) who filled in the SWAL-QOL had a score above the cut-off value. At 10-year plus follow-up, this was the case for 8 of the 14 patients (57%).

Overall, the results suggest that at 10-year plus follow-up, patients have only minor problems in voice/speech-related quality of life. Median VHI scores slightly worsened from 2 to 5, indicating a little more voice-related problems in daily life, while maximum scores improved from 91 to 47, indicating voice-related quality of life of patients with the worst VHI scores improved. Also, at both 6- and 10-year

FIGURE 1 Flow chart with patient numbers at all follow-up moments and reasons for exclusion

plus follow-up four patients had a VHI score above the cut-off value (of whom three were the same patients). The patients with a VHI score above the cut-off had tumors of mixed localizations (hypopharynx [$n = 2$], oropharynx [$n = 1$], and nasopharynx [$n = 1$]). Subjective speech (based on the median SHI) remained stable, while maximum SHI scores also improved from 92 to 47. Of the six patients that currently had an SHI above the cut-off value indicating speech problems in daily life, only four had an SHI above cut-off value at last follow-up. Of the six patients with SHI scores above the cut-off value, three had an hypopharyngeal tumor, two an oropharyngeal tumor, and one had a nasopharyngeal tumor.

EQ-5D-5L scores slightly increased from 6- to 10-year plus follow-up, indicating a lower quality of life, although the median EQ-VAS scores were more or less equal (85 [range 60-100] and 88 [range 50-100], respectively). At 6-year follow-up 2 (14%), 0 (0%), 2 (14%), 5 (36%), and 4 (29%) patients reported problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression, respectively. At 10-year plus follow-up, this was the case in 4 (29%), 1 (7%), 6 (43%), 4 (29%), and 4 (29%) patients, respectively.

4 | DISCUSSION

Given the increasing survival rates of patients treated for HNC, due to changing etiology and continuously improving treatment strategies, knowledge of long-term functional outcomes had gained importance.¹⁹ This is the first study to report on functional outcomes and quality of life of patients more than 10 years after IMRT with concurrent chemotherapy for HNC combined with preventive rehabilitation exercises, which is quickly becoming current practice at a rising number of institutes. In our cohort, objective swallowing problems were minimal, with slight deterioration compared to the results at 6-year follow-up assessment. None of the evaluable patients at 10-year plus follow-up were feeding tube dependent, consumed a modified diet (FOIS <7) or had suffered from pneumonia since the 6-year follow-up. However, subjective swallowing-related quality of life moderately worsened according to SWAL-QOL scores. None of the patients had or perceived trismus. Subjective and objective voice- and speech-related outcomes stayed more or less stable from 6- to 10-year follow-up. Overall quality of

TABLE 1 Baseline characteristics of patients evaluable at 10-year plus follow-up (n = 14)

		Number of patients (%)
Gender	Male	11 (79)
	Female	3 (21)
Age at baseline Median (range)		58 (39-66)
Tumor site	Oral cavity/oropharynx	8 (57)
	Larynx/hypopharynx	4 (29)
	Nasopharynx	2 (14)
T classification	T1	3 (21)
	T2	7 (50)
	T3	4 (29)
	T4	0 (0)
N classification	N0	1 (7)
	N1	5 (36)
	N2	5 (36)
	N3	3 (21)
AJCC stage	II	0 (0)
	III	6 (43)
	IV	8 (57)
Rehabilitation	Without TheraBite	5 (36)
	With TheraBite	9 (64)

Abbreviations: AJCC stage, American Joint Committee on Cancer stage seventh edition; RT, radiotherapy.

life remained at a high level, according the EQ-VAS assessment, although a third of the patients experienced at least some pain or discomfort. The results suggest that with current practice, including IMRT and preventive rehabilitation exercises, the functional outcomes and quality of life of patients surviving more than 10 are reasonably well-maintained.

The worsening observed in, predominantly subjective, functional outcomes might be caused by multiple factors. Firstly, aging likely plays a role in the deterioration of swallowing (efficiency), and speech, function over time.⁴⁴ Multiple studies have shown that older individuals have less effective swallowing function compared to younger adults.⁴⁵ Secondly, late treatment effects such as neuropathy and continuing fibrosis of swallowing muscles are a known cause of late functional problems after radiotherapy for HNC.^{21,22} The mechanism of this continuing fibrosis is probably based on a continuous (over)production of factors activating wound healing, which continues until long after the initial radiotherapy.²² Also, since the resolution of the videofluoroscopy studies was better at 10-year follow up, minimal aspiration might have been missed at 6-year follow-up. There were some discrepancies between subjective and objective outcomes. For example, the median MIO decreased with 6 mm

between 6- and 10-year plus follow-up which did not result in any of the patients with either clinical trismus or perceived trismus. The four patients with perceived trismus at the 6-year mark, did not perceive their mouth opening as decreased while either mouth opening was stable (n = 2) or decreased (n = 2). This might be due to a very gradual decrease in median MIO, which enables habituating to and coping with the new situation. This was not true, however, for swallowing; the moderately deteriorated swallowing-related quality of life as measured by the SWAL-QOL was not accompanied by worsened objective measures, which stayed stable or even improved. This might be because subjective measures are more sensitive to small deteriorations in swallowing function than objective measures.

Some earlier studies have investigated long-term functional outcomes after CRT. Kraaijenga et al published 10-year results of a historical cohort treated with CRT for HNC at our institute between December 1999 and November 2004.^{29,46,47} During this time period IMRT was applied less often (50% vs 100%) and no preventive rehabilitation interventions were offered. When our results are compared to that cohort, aspiration was observed less often (30% in our study vs 68% in the study of Kraaijenga et al), as well as contrast residue (70% vs 100%). Also, less patients were feeding tube dependent (0% vs 14%), had pneumonia the past 6 months (0% vs 14%) and had an FOIS below 7 indicating a modified diet (0% vs 55%). To properly appreciate the difference in functional outcomes, one should keep in mind that the patients of the historical cohort were somewhat older (median 63 [range 42-74] vs 58 [range 39-66] in our study), and had more stage IV tumors (68% vs 57%). Yet, the differences likely also reflect the improvement resulting from more advanced radiotherapy in combination with preventive rehabilitation.

Besides this historical cohort treated at our institute, other studies have also reported on long-term swallowing-related outcomes after CRT for HNC without preventive rehabilitation.⁴⁸⁻⁵⁰ All of these studies report that severe late toxicity is common after CRT for HNC. Machtay et al found that 99 of the 230 patients (34%) at a median follow-up of 3 years after CRT (no IMRT) for HNC experienced late toxicity.⁴⁸ Rutten et al concluded that 57% of the 77 analyzed CRT for HNC patients (of whom 17% received IMRT) had impaired swallowing and 23% had silent aspiration at a median follow-up of 3.7 years after CRT for HNC.⁴⁹ Only 15.6% reported to have a normal diet. Frowen et al analyzed 39 patients after CRT (no IMRT) for HNC and found that at 5 years after treatment, 2 patients (5%) were PEG tube dependent.⁵⁰ Hutcheson et al published results from the longest follow-up on swallowing function after CRT (7% IMRT) for HNC.²¹ They also reported a high prevalence of impaired swallowing at 9 years post (C)RT,

TABLE 2 Swallowing-related outcomes at 6- and 10-year plus follow-up of patients evaluable at 10-year plus follow-up (n = 14)

	Number of patients (%)			
	6-year follow-up	95% CI	10-year plus follow-up	95% CI
Objective outcomes				
DIGEST grade based on VFS (n = 10)				
Safety grade 0	8 (80)	49-94	7 (70)	40-89
Safety grade 1	2 (20)	6-51	1 (10)	2-40
Safety grade 2	0 (0)	0-28	1 (10)	2-40
Safety grade 3	0 (0)	0-28	1 (10)	2-40
Safety grade 4	0 (0)	0-28	0 (0)	0-28
Efficiency grade 0	1 (10)	2-40	0 (0)	0-28
Efficiency grade 1	6 (60)	31-83	4 (40)	17-69
Efficiency grade 2	1 (10)	2-40	1 (10)	2-40
Efficiency grade 3	2 (20)	6-51	5 (50)	24-76
Efficiency grade 4	0 (0)	0-28	0 (0)	0-28
DIGEST grade 0	1 (10)	2-40	0 (0)	0-28
DIGEST grade 1	7 (70)	40-89	5 (50)	24-76
DIGEST grade 2	2 (20)	6-51	3 (30)	11-60
DIGEST grade 3	0 (0)	0-28	2 (20)	6-51
DIGEST grade 4	0 (0)	0-28	0 (0)	0-28
Pneumonia since six-year follow-up	0 (0)	0-22	0 (0)	0-22
Feeding tube dependent	0 (0)	0-22	0 (0)	0-22
Modified diet (FOIS <7)	0 (0)	0-22	0 (0)	0-22
Weight in kg Median (range)	76 (68-103)	69-89	77 (70-103)	72-85
Pain (VAS) Median (range)	0 (0-25)	0-12	0 (0-30)	0-4
Subjective outcomes				
Perceived				
Xerostomia	10 (71)	45-88	10 (71)	45-88
Difficulty swallowing	7 (50)	27-73	10 (71)	45-88
Difficulty masticating	1 (7)	1-31	3 (21)	8-48
Problems with				
Oral transport with solids	2 (14)	4-40	6 (43)	21-67
Oral transport with thick liquids	1 (7)	1-31	2 (14)	4-40
Oral transport with thin liquids	0 (0)	0-22	0 (0)	0-22
Swallowing problems with solids	7 (50)	27-73	9 (64)	39-84
Swallowing problems with thick liquids	1 (7)	1-31	3 (21)	8-48
Swallowing problems with thin liquids	0 (0)	0-22	2 (14)	4-40

Abbreviations: CI, confidence interval; DIGEST, Dynamic Imaging Grade of Swallowing Toxicity; FOIS, functional oral intake scale; MIO, maximal inter-incisal opening; VAS, visual analog scale; VFS, videofluoroscopy.

with 66% being gastrostomy dependent,²¹ although this result might not be representative for all HNC patients receiving CRT, because the patients included in their analysis were complaining about dysphagia and specifically referred for a modified barium swallow.

Long-term speech-related outcomes after CRT for HNC are scarce in literature.⁵¹ Results suggest that speech

problems are common after CRT, but extensive long-term (10-year) evaluations are lacking.^{52,53} Kraaijenga et al published voice- and speech-related outcomes of the previously mentioned historical cohort 10-years after CRT.⁵⁴ Voice and speech problems were common in that cohort, with 68% and 77% of the 22 evaluated patients reporting voice and speech problems in daily life, based on VHI and SHI scores above

TABLE 3 Trismus related outcomes at 6- and 10-year plus follow-up of patients evaluable at 10-year plus follow-up (n = 14)

	Number of patients (%)			
	6-year follow-up	95% CI	10-year plus follow-up	95% CI
Objective outcomes				
Mouth opening in mm Median (range)	51 (36-70)	39-65	45 (36-68)	38-60
Trismus (MIO <36 mm)	0 (0)	0-22	0 (0)	0-22
Subjective outcomes				
Perceived deteriorated mouth opening	4 (29)	12-55	0 (0)	0-22

Abbreviations: CI, confidence interval; FOIS, functional oral intake scale; MIO, maximal inter-incisal opening; VAS, visual analog scale.

TABLE 4 Voice and speech related outcomes at 6- and 10-year plus follow-up of patients evaluable at 10-year plus follow-up (n = 14)

	Number of patients (%)			
	6-year follow-up	95% CI	10-year plus follow-up	95% CI
Objective outcomes				
AVQI ¹⁻⁸ Median (range)	4.7 (3.7-6.1) ^a	NA ^a	3.9 (1.6-8.0)	2.4-5.3
ALF-PPFs (0-100) Median (range)	85 (67-92) ^a	NA ^a	75 (69-87)	69-86
Subjective outcomes				
Perceived different voice	8 (57)	33-79	7 (50)	27-73

Note: VHI and SHI scores of respectively 13 and 12 subjects were available at 6-year follow-up.

Abbreviations: ALF-PPFs, alignment-free phonological and phonemic features with higher values indicating better intelligibility; AVQI, Acoustic Voice Quality Index with lower values indicating better voice quality; CI, confidence interval; CRT, chemoradiotherapy.

^aValues from earlier publication of Kraaijenga et al. Analyses on speech recordings could not be repeated.

the cut-off values. In the present cohort, there were less patients with scores above the cut-off value (29% and 43% for VHI and SHI). Again, comparisons between these two different cohorts of the NKI-AVL should be interpreted with caution since differences might be caused by preventive rehabilitation strategies, but might also be due to differences in patient and tumor characteristics. The median intelligibility deteriorated from 85% to 75% in this cohort. This might be, just as the deterioration of swallowing function, caused by continuing fibrosis or the effects of aging, which both affect structures of the upper aerodigestive tract.

While the benefit of IMRT over conventional RT is not disputed, it has been challenging to substantiate the benefit of preventive rehabilitation in clinical research. Recently, a Cochrane review by Perry et al on preventive exercises was published.¹³ They concluded that the evidence supporting the effectiveness of preventive exercises on functional outcomes post treatment was not yet convincing. The lack of convincing evidence is not necessarily due to the lack of observed effectiveness, but is caused by the limited sample sizes of the included studies, resulting in limited power and therefore imprecise estimates of effect, and the impossibility of meta-analysis due to the dissimilarities in outcome measures used. An important issue with this review is that it did not consider the relevance of patient compliance to the exercises. Individual studies do suggest positive effects

of preventive exercises with superior swallowing function when compared to (historical) controls.^{6-9,11,14} Moreover, patients who maintain their oral intake during CRT have favorable outcomes compared to patients who become tube dependent.^{55,56} These findings support the preposition that both the exercises and the maintenance of oral intake prevent decreased use, and thereby they may prevent nonuse atrophy of swallowing muscles, which is the rationale behind preventive strategies.

4.1 | Limitations

The main limitation of this study is the small sample size, with only 14 of the 22 patients at the 6-year follow-up still alive and evaluable at 10-year plus. It is, however, not an uncommon sample size given the survival rate in advanced HNC. Also, DIGEST grades were assessed on the video-fluoroscopy studies including only four bolus trials instead of 10 bolus trials on which the grading system was validated.

5 | CONCLUSION

Functional status and quality of life of patients treated for advanced HNC with state-of-the-art CRT and

TABLE 5 Quality of life related outcomes at 6- and 10-year plus follow-up of patients evaluable at 10-year plus follow-up (n = 14)

	Number of patients (%)			
	6-year follow-up	95% CI	10-year plus follow-up	95% CI
SWAL-QOL (0-100) Median (range)				
General burden	0 (0-88)	0-25	25 (0-63)	0-50
Food selection	0 (0-75)	0-25	7 (0-38)	0-25
Eating duration	38 (0-75)	0-50	38 (0-63)	13-50
Eating desire	8 (0-75)	0-33	21 (0-58)	0-33
Fear of eating	8 (0-75)	0-33	25 (0-69)	6-44
Sleep	25 (0-75)	0-50	38 (0-75)	25-63
Fatigue	17 (0-67)	0-42	38 (0-58)	8-50
Communication	0 (0-100)	0-50	25 (0-50)	0-50
Mental health	0 (0-70)	0-25	10 (0-50)	0-35
Social function	0 (0-50)	0-25	10 (0-40)	0-25
Symptom score	21 (0-59)	5-45	21 (0-41)	4-36
Total score	12 (0-58)	0-28	22 (0-41)	2-34
Swallowing problems in daily life based on SWAL-QOL ≥ 14	5 (38)	18-64	8 (57)	33-79
VHI Median (range)				
Voice domain (0-56)	2 (0-42)	0-22	5 (0-32)	0-25
Psychosocial domain (0-56)	0 (0-47)	0-5	0 (0-13)	0-10
Total score (0-120)	2 (0-91)	0-31	5 (0-47)	0-30
Voice problems in daily life based on VHI ≥ 15 N (%)	4 (31)	13-58	4 (29)	12-55
SHI Median (range)				
Speech domain (0-56)	3 (0-45)	0-27	3 (0-34)	0-20
Psychosocial domain (0-56)	0 (0-44)	0-11	0 (0-11)	0-10
Total score (0-120)	3 (0-92)	0-44	3 (0-47)	0-29
Speech problems in daily life based on SHI ≥ 6 N (%)	4 (33)	14-61	6 (43)	21-67
EQ-5D-5L dimension; problems with:				
Mobility	2 (14)	4-40	4 (29)	12-55
Self-care	0 (0)	0-22	1 (7)	1-31
Usual activity	2 (14)	4-40	6 (43)	21-67
Pain/discomfort	5 (36)	16-61	4 (29)	12-55
Anxiety/depression	4 (29)	12-55	4 (29)	12-55
EQ-VAS (0-100) Median (range)	85 (60-100)		88 (50-100)	

Note: SWAL-QOL scores of respectively 13 and 14 subjects were available at 6- and 10-year follow-up.

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQoL-5D-5L; EQ-VAS, EuroQoL Visual Analog Scale; SHI, speech handicap index; VHI, voice handicap index.

preventive rehabilitation exercises who have survived 10 or more years is reasonably well-maintained. Swallowing, trismus and speech related outcomes only moderately deteriorated from 6- to 10-years, with a perceived excellent overall quality of life.

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APPENDIX 1

APPENDIX A1 Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scoring system