



Adherence to preventive swallowing exercises for head and neck cancer patients undergoing (chemo)radiotherapy treatment

Sara Fredslund Hajdú^a , Malene Bæk Christensen^{b,c,d,*}, Marlene Østermark Kristensen^{b,*}, Irene Wessel^e , Christoffer Johansen^{f,g} and Susanne Dalton^g

^aDepartment of Occupational Therapy & Physiotherapy, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark; ^bFaculty of Health & Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ^cDepartment of Occupational Therapy & Physiotherapy, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark; ^dCopenhagen Centre for Cancer and Health, Copenhagen, Denmark; ^eDepartment of Otorhinolaryngology Head and Neck Surgery & Audiology, University Hospital of Copenhagen, Copenhagen, Denmark; ^fDepartment of Oncology, University Hospital of Copenhagen, Rigshospitalet Copenhagen, Denmark; ^gUnit of Survivorship, Danish Cancer Society Research Center, Copenhagen, Denmark

ABSTRACT

Background: In recent years, preventive swallowing exercises have been investigated as a means to limit dysphagia in head and neck cancer patients. However, adherence to exercise regimes has been poorly documented limiting the conclusions drawn on the effects of the interventions. We investigated adherence to a preventive swallowing exercise program and identified possible associations between adherence and four selected baseline factors: HPV status, partner status, concomitant chemotherapy and tumor site and between adherence to swallowing exercises and attendance to supervised training sessions.

Material and methods: Forming part of an ongoing RCT (clinicaltrials.gov NCT02385929) adherence to intervention was based on participant provided training-logs. The exercise program consisted of 3 weekly supervised sessions of 30 min each and a home-based exercise program to be performed three times daily. Adherence was calculated as percentage of prescribed exercises completed and dichotomously as high ($\geq 80\%$ ~median) and low ($< 80\%$ ~median) adherence. Associations between adherence and clinical/demographic factors (HPV, partner status, chemotherapy, tumor site or attendance level) were explored by logistic regression analyses.

Results: Full adherence data were available from 45 (76%) participants. The total cohort median adherence to exercises was 78%. No association was found between any of the tested factors and adherence.

Discussion: The study found a high adherence to preventive swallowing exercises in HNC patients undergoing (chemo)radiotherapy, both in home-based exercises and in supervised sessions, when compared to other studies, although median adherence to home-based exercises was below the defined 80% threshold. We acknowledge, that adherence in an RCT may be higher than in the everyday clinical situation due to surveillance bias. However, we find it reassuring that HNC patients comply with a preventive swallowing program, which requires some time investment from the patients.

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Introduction

As treatment improves and survival rates increase, a raising number of people with head and neck cancer (HNC) are cancer survivors living with the effects of the treatment [1]. Previous studies have shown that late effects, especially oropharyngeal dysphagia, have a negative impact on convalescence and quality of life (QoL) [2–4]. Several clinical intervention studies have investigated the effect of preventive swallowing exercises in HNC patients and find only minimal effects on dysphagia or the results are inconclusive [5,6]. Meanwhile, there are limited analyses of patients' adherence to preventive swallowing exercise programs. With lacking positive results consensus on appropriate measures and cutoff values have not yet been reached, resulting in

varying methods used to report adherence [7–13]. This raises the question whether the lack in effect is directly linked to the exercise programs themselves or if it is rather due to low adherence, which must be considered an essential factor when evaluating the impact of any exercise program.

Meanwhile, the demography of HNC patients is changing. While the dominating risk factors for cancer in the larynx, hypo- and oropharynx and oral cavity are still excessive tobacco and alcohol consumption, HPV-induced cancer incidence continues to increase and oropharyngeal cancer now represents the largest group of head and neck associated cancers in Denmark [14]. HNC patients with p16-positive tumors are typically of a higher socioeconomic status and have a healthier lifestyle and better long-term survival than patients with p16-negative tumors [3,15,16]. Further, these

patients score higher on QoL, speech and swallowing function both at baseline and post treatment [3,17]. In line with these results, HNC patients who live with a partner tend to experience less late effects after radiotherapy compared to patients who live alone [18], and marriage has been associated with improved survival among HNC patients [19].

Despite an overall frame for treatment regimen, the treatment strategy is always planned on an individual basis. Factors such as tumor stage, tumor site, age, performance status, and lifestyle will influence radiation dosage, the tissues affected, whether concomitant chemotherapy is offered, side effects, treatment effect and prognosis. Hence, it is relevant to look at possible associations between adherence and demographic and clinical data to evaluate if certain characteristics may predict low adherence and, consequently, poor effect of the exercises. Knowing possible associations between clinical and/or demographic factors and adherence may enable clinicians to personalize future swallowing therapy.

The current study is an evaluation of the adherence to a preventive swallowing exercise program in an ongoing randomized controlled trial (clinicaltrials.gov NCT02385929) [20]. Here we explore to what degree participants in the intervention group were adherent to the swallowing exercises. Further we explore possible associations between adherence to swallowing exercises and demographic and clinical data. While identifying associations was not the primary aim of this study we limited it to explore only a few factors. As patients with lower educational level and income are found to have increased morbidity and mortality after cancer treatment due to poorer health behavior compared to patients with higher socio-economic status [21] it is relevant to know if HPV is also a determining factor in adherence to swallowing therapy. Further, the support from a cohabitating partner may be beneficial when finding motivation to control side effects of HNC treatment, e.g., adhere to a swallowing exercise routine [4]. Meanwhile, the individualization of the exercise program was considered an important part of the protocol with the purpose to keep participants engaged in the intervention throughout radiotherapy treatment. Hence, it was hypothesized that HPV positive, living with a partner and high attendance at supervised sessions, would influence adherence positively.

Concomitant chemotherapy, compared to radiotherapy alone, was hypothesized to negatively influence adherence due to higher toxicity and increased risk of nausea and fatigue as also seen in other studies [10,11]. Likewise, because of its influence on both type and severity of side effects, and the treatment provided, tumor location was an obvious factor to explore for association. Based on clinical experience, we hypothesized that patients with laryngeal cancer experience more severe pain when swallowing, and that this would influence adherence negatively compared to pharyngeal and oral cancers.

Material and methods

This study forms part of a 2-armed RCT that explores the effects of a preventive swallowing and resistance training

program on swallowing function, physical function and QoL (SYNK trial) [20]. The trial was powered for 120 participants in each group, i.e., usual care or intervention.

Participants

Participants for the SYNK trial were recruited from the oncology departments at respectively Copenhagen University Hospital Rigshospitalet and Naestved Hospital, Denmark. Adults diagnosed with cancer in the oral cavity, larynx, oropharynx, hypopharynx or unknown primary tumor and planned for (chemo)radiotherapy with curative intent were invited to participate. Patients who had primary surgery with postoperative (chemo)radiotherapy were also included. Exclusion criteria were (1) physical, social or cognitive conditions that would hinder participation in intervention, (2) non-Danish speaking, and (3) previous HNC treatment.

Preventive swallowing exercises

Participants in the intervention group were asked to complete swallowing exercises as described in the SYNK protocol [20]. Based on a clinical examination of swallowing function the exercise programs were designed individually from a selection of 14 exercises (tongue stretching and strengthening, jaw mobility and mouth opening, Mendelsohn maneuver, Shaker exercise, Masako maneuver, Effortful swallow and Valsalva). To assess the participant's baseline eating-, drinking-, and swallowing ability the clinical examination was focused on breathing (efficiency and coordination with swallow), body position, facial expressions (coordination and strength), voice (alterations), and cough (efficiency and coordination). The examination was performed by an occupational therapist (OT) and consisted of observations, visual and tactile examination and, when necessary, screening of oral intake. Exercises were prescribed at 10 repetitions, three cycles per day (1 cycle = 10 repetitions of one exercise), 7 d per week during radiotherapy. Thus, participants were prescribed a minimum of one exercise (3 cycles) and a maximum of 14 exercises (42 cycles) per day. Further, patients at risk of aspiration were asked to use the Supraglottic swallowing technique. Based on continuous clinical evaluation exercises could be added or distracted by the OT. Besides home-based exercises participants were asked to come in for individual training sessions supervised by OT three times per week. Thirty minutes were allotted for each session, though with room to accommodate specific needs.

Participants were included as soon as possible after diagnosis but not all participants were baseline tested and randomized before radiotherapy began. This caused variabilities in possible training days.

Baseline demographic and clinical factors

Relevant demographic data were collected for all participants. This included age, sex, disease stage, treatment type (radiotherapy ± chemotherapy and/or surgery), tumor site (oropharynx, hypopharynx, cavum oris, larynx), HPV (p16

positive versus negative) and partner status (single versus in a relationship versus living with partner), alcohol consumption, smoking history, educational level, and affiliation to work market.

Adherence

Adherence to the swallowing exercise program was collected prospectively. Participants in the intervention group were provided a training logbook to log their daily training. One mark in the training log indicated the completion of one cycle. Participants were asked to bring the training-log to each supervised training session of which the responsible OT recorded participants' *attendance*. In the following *adherence* refers to the completion of home-based exercises only.

Statistical analysis

Demographic data were reported descriptively. Adherence was reported descriptively in two ways: percent exercises completed determined as the total number completed exercises in relation to total number of prescribed exercises; and as a dichotomous outcome of low practice (<80%) or high practice (\geq 80%). Likewise, attendance data were reported as percent attended training sessions determined as total number of attended sessions in relation to total number of training appointments with OT, and as a dichotomous outcome of low attendance (<80%) or high attendance (\geq 80%). As adherence and attendance data was skewed they are presented by median rather than mean. The cutoff value of 80% were set high to be as true to the protocol as possible while acknowledging that some deviation is acceptable given the intensive and demanding treatment regimen and exercise program which also prescribed progressive resistance training twice weekly.

Lastly, average weekly adherence was reported by median percentage for each week of radiotherapy for the total cohort.

Simple logistic regression analyses were conducted to explore associations between adherence and clinical/demographic data (HPV, treatment, partner status, tumor site and attendance) with adherence (high versus low) as the dependent variable. The model was adjusted for age and sex. The regression analyses were reported by odds ratio (OR) with 95% confidence interval (CI). Significance was set at $p \leq .05$. All statistical analyses were conducted using the Statistical Package for the Social Science (SPSS) software version 24 (SPSS, Chicago, IL).

Ethics and data protection

The SYNK trial was approved by the Research Ethics' Committee of the Capital Region, Denmark (H-2-2014-074) and the Danish Data Protection Agency (301378). The trial is registered at clinicaltrials.gov: NCT02385929. All participants signed an informed consent upon inclusion.

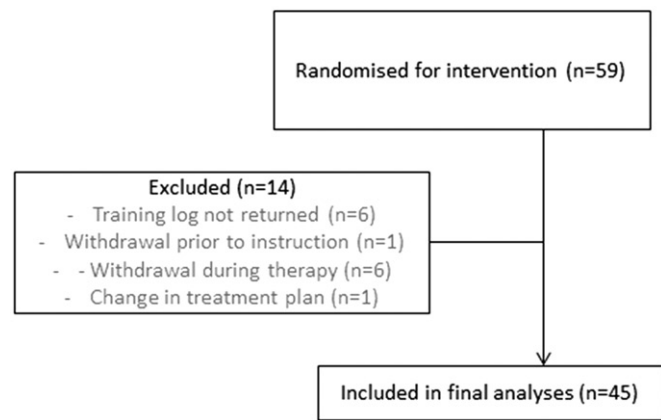


Figure 1. Flowchart.

Results

When conducting the present study, half of the participants aimed for in the power calculation had been recruited into the trial, of which 59 were randomized to intervention group. Six participants dropped out during therapy (three after first OT session, three during first half of radiotherapy), one dropped out prior to instruction, one participant had treatment regimen changed thus not fulfilling inclusion criteria and finally six participants did not return their training log. This provided 45 (76%) participants with full adherence data (Figure 1). Demographic details of the 45 participants and of the six who did not return their training logs are shown in Table 1.

Adherence to swallowing exercises and supervised sessions

Of the 45 participants, 21 (47%) presented with high adherence level (\geq 80%). The total sample had a median adherence level of 78% with interquartile range of [31%; 96%]. On average, participants' training periods stretched over 35 days (5 weeks) ranging from 28 to 46 days. First swallowing session occurred between first and eighth day of radiotherapy (day 3 on average). Participants were prescribed an average of 694 cycles of swallowing exercises ranging from 417 to 1932 cycles in total during their radiotherapy treatment. Average daily prescribed cycles were 19.4 (6.5 unique exercises of three cycles), ranging from 12 to 42 (4–14 unique exercises prescribed). Seven participants (17%) kept the same number of prescribed exercises throughout intervention period. Four (9%) had less exercises prescribed by the end of intervention than at the beginning. The remaining 34 participants were prescribed additional exercises over time. Over time adherence to exercise program ranged between 95% (week 2) and 74% (week 6) as shown in Figure 2. Changes over time were not tested for significance.

Attendance data was missing on four of the 45 participants. Of the remaining 41 participants 59% ($n=24$) attended all supervised training sessions providing a median of 100%. Attendance levels ranged between 53% and 100% with 35 of participants (85%) presenting with a high attendance level (\geq 80%).

Table 1. Demographic and clinical data.

	Included in analysis <i>n</i> = 45 (%)	Training-log not returned <i>n</i> = 6 (%)
Mean age at inclusion in years [range]	62 [41–87]	61 [48–73]
Age (years)		
≤49	3 (7)	2 (33)
50–59	19 (42)	1 (17)
60–69	16 (35.5)	1 (17)
≥70	7 (15.5)	2 (33)
Sex		
Male	35 (78)	6 (100)
Female	10 (22)	–
Tumor site		
Oral cavity	3 (7)	1 (17)
Oropharynx	24 (53)	4 (67)
Hypopharynx	4 (9)	1 (17)
Larynx	15 (31)	–
Disease stage		
I	7 (16)	1 (17)
II	6 (13)	–
III	5 (11)	2 (33)
IV	27 (60)	3 (50)
Treatment		
Radiotherapy only	16 (36)	1 (17)
Surgery with postoperative radiotherapy	2 (4)	1 (17)
Concomitant chemo- and radiotherapy	25 (56)	3 (50)
Surgery with postoperative chemo- and radiotherapy	2 (4)	1 (17)
Partner status		
Single	11 (24.5)	3 (50)
In a relationship, living alone	5 (11)	–
Living with partner	29 (64.5)	3 (50)
HPV status		
p16 positive	20 (45)	4 (67)
p16 negative	21 (47)	2 (33)
Unknown	4 (8)	–
Smoking history		
Current	8 (18)	1 (17)
Used to smoke	31 (69)	3 (50)
Never smoked	6 (13)	2 (33)
Alcohol consumption		
Do not consume alcohol	12 (27)	–
1–7 units per week	16 (36)	1 (17)
8–14 units per week	6 (13)	4 (67)
15–20 units per week	7 (15)	1 (17)
≥21 units per week	4 (9)	–
Highest educational level		
Short ^a	9 (20)	2 (33)
Medium ^a	12 (27)	2 (33)
High ^a	21 (47)	2 (33)
Missing	3 (6)	–
Affiliation to work market		
Wage earner, full time	16 (36)	3 (50)
Wage earner, part time	1 (2)	–
Self employed	3 (7)	–
Sick leave	3 (7)	1 (17)
Regular pensioner	18 (40)	2 (33)
Student, apprentice	1 (2)	–
Missing	3 (6)	–

^aShort education: primary through lower secondary; medium education: upper secondary; high education: tertiary.

Association between adherence and clinical/demographic factors

The regression analyses of association between clinical/demographic factors and adherence are shown in Table 2. No significant association was found for any of the five included variables. Adjusting for sex and age did not change the results.

Post hoc analyses were made to explore the possible influence of the six missing training logs in two scenarios; one where the six participants had low adherence and one where all six had high adherence. Logistic regression was run on four of the five variables (all except attendance).

Including the six missing training logs in the analyses did not provide the results with any statistically significant predictors of high adherence.

Discussion

The total median adherence to the preventive home-based swallowing exercises was 78%. Although high for this type of study it did not pass the 80% cutoff value defined in current study. However, comparing studies – the current one included – is challenging as the interventions with regards to intensity, frequency, type and number of exercises and the

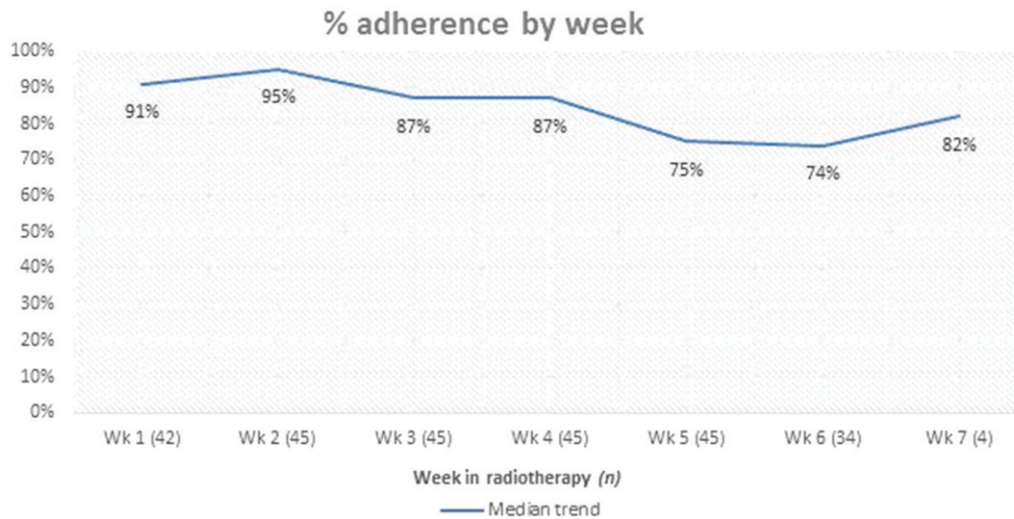


Figure 2. Adherence over time.

Table 2. Simple regression analysis of association between adherence and clinical/demographic data ($n = 47$).

	Adherent, n (%)	Non-adherent, n (%)	Un-adjusted		Adjusted for sex and age	
			OR [CI]	<i>p</i>	OR [CI]	<i>p</i>
HPV status^a						
p16-positive	9 (45)	11 (55)	1.33 [0.38; 4.62]	.65	1.24 [0.35; 4.41]	.74
p16-negative	8 (38)	13 (62)	Reference group		Reference group	
Partner status						
In a relationship, living alone	2 (40)	3 (60)	0.56 [0.07; 4.76]	.59	0.50 [0.06; 4.58]	.54
Cohabiting	13 (45)	16 (55)	0.68 [0.17; 2.73]	.58	0.71 [0.16; 3.07]	.64
Single	6 (55)	5 (45)	Reference group		Reference group	
Attendance^a						
High \geq 80%	17 (49)	18 (51)	1.89 [0.31; 11.68]	.49	1.76 [0.28; 11.00]	.55
Low $<$ 80%	2 (33)	4 (67)	Reference group		Reference group	
Treatment						
Radio- and chemotherapy	11 (41)	16 (59)	0.55 [0.17; 1.84]	.33	0.38 [0.10; 1.52]	.17
Radiotherapy	10 (56)	8 (44)	Reference group		Reference group	
Tumor site						
Oral cavity	1 (33)	2 (67)	0.38 [0.03; 5.17]	.46	0.22 [0.01; 4.20]	.31
Oropharynx	11 (46)	13 (54)	0.64 [0.17; 2.40]	.50	0.52 [0.13; 2.10]	.36
Hypopharynx	1 (25)	3 (75)	0.25 [0.02; 3.04]	.28	0.22 [0.02; 2.78]	.24
Larynx	8 (57)	6 (43)	Reference group		Reference group	

^a $n = 41$.

OR: odds ratio; CI: confidence interval, 95%.

methods used to measure adherence vary considerably [7–13].

In our study, the highest adherence was observed during the second week of radiotherapy (95%). Over the following weeks, adherence dropped until reaching its lowest average adherence at 74% in week six of radiotherapy. This fluctuating tendency was also found in other similar studies [8,10,11]. Reasons for the decreasing adherence were not investigated but plausible explanations may be the simultaneous increase in side effects to treatment. Shinn et al [12] found that 51% were fully or partially adherent to preventive swallowing exercises during radiotherapy and that typical reasons for non-adherence were (1) not understanding the importance of the exercises; (2) radiotherapy induced side effects; and (3) forgetfulness. Shinn et al. [12] only offered exercise instructions three times during radiotherapy whereas in the SYNK trial, supervised sessions are scheduled three times per week

amounting to a total of up to 20 individual sessions during radiotherapy, depending on the duration of radiotherapy treatment. The aim of consistent and frequent supervision was to continuously ensure correct performance of the exercises and facilitate an understanding of the importance of the intervention. Assuming this aim was met, the reasons for non-adherence are more likely to be found in the side effects to radiotherapy that can interfere with motivation and ability to perform the exercises, e.g., pain, nausea, xerostomia, and fatigue. Typically, side effects kick in during second or third week of radiotherapy and from then on, increase day by day. Opioids are often necessary for pain management [22]. Until pain is adequately or tolerably under control patients may experience some demotivation regarding training activities. This could explain the decrease in adherence followed by a slight increase, although adherence by weeks 6 and 7 were based on fewer participants (34 and 4, respectively). The

changes in adherence over time were not tested for significance. Yet, this aspect of adherence is highly relevant to consider when planning therapeutic interventions. The decreasing adherence may exactly be an indicator of important time points when extra attention is necessary to support the patient in complying with a given exercise program.

In regard to the secondary aim of the study: to determine clinical/demographic factors' influence on adherence, none of the explored factors (HPV, tumor site, concomitant chemotherapy, partner status, and attendance) showed significant association with adherence level, neither in the unadjusted analyses nor when adjusting for sex and age. The negative results could be a consequence of the relatively small sample size, or it could be because the exercise programs were individually planned thus seemed relevant to the participants and the motivation they brought into the intervention regardless of external factors. Lastly, HPV, tumor site, partner status, and chemotherapy may not have been an exact expression of the assumed qualities. I.e., HPV status may not have reflected participants' socio-economic position, let alone motivation to prophylactic exercise. Probably, the type and severity of side effects, which is influenced by not only tumor location but by treatment modality, health behavior, disease stage, etc., influences adherence much more than tumor site itself. Living with a partner did not necessarily enhance adherence better than the support gained from other social support networks. And although chemotherapy increases toxicity the analysis did not take into account that patients who receive concomitant chemotherapy are generally healthier and younger. Attendance to supervised sessions was good with the majority attending all sessions. It should be noted that the supervised sessions in the SYNK trial were scheduled in continuation of participants' radiotherapy treatment, thus avoiding unnecessary waiting time or extra visits to the hospital. Assumingly this have contributed to the high attendance ($n=35$ (85%) attending $\geq 80\%$ of possible sessions, Table 2) although reasons are likely to be influenced by multiple factors not covered in current study. Despite the high attendance, which had the purpose to enhance understanding of the exercises and the importance of the intervention, it was not associated with higher adherence. However, with the lowest attendance being 53% and only six participants (13%) with attendance below the 80% threshold an association would be difficult to establish. This may have been influenced by the small study sample. With a median adherence of 78% the results may still suggest that the frequent supervision and individualized exercise prescription has a decisive effect on adherence. In accordance, Govender et al. [23] found that appointments with a therapist and motivational support enhanced adherence to a swallowing exercise program among HNC patients. Also, Perry et al. [6] pointed out that the exercise burden in preventive swallowing trials for HNC patients often become so onerous that it causes patients to drop out of the trials. By intentionally avoiding the 'one size fits all' strategy and instead planning each exercise program individually, the SYNK trial may have been able to prevent such drop-outs and demotivation due to the exercise programs per se. As

seen, some participants were prescribed an average of only four different exercises whereas other participants were prescribed the full program of 14 exercises. The protocol also allowed for the OT to add extra exercises and extract others over time. It would have been relevant to explore if the number of prescribed exercises affected adherence levels, however this was beyond the scope of this paper. In future analyses, it would also be relevant to explore the reasons for drop-outs in the intervention group, let alone the clinical and demographic characteristics of those participants. So far, we hypothesize that the individualization alongside frequent supervision and explanations of the rationale of the exercise program improved participants' perception of relevance, and in turn their motivation and adherence to intervention.

Some limitations of current study should be noted. First, measuring adherence linearly rather than dichotomously would have provided a more nuanced interpretation of adherence. Second, adherence data rely solely on participant information. As per Shinn et al. [12], self-reporting carries a high risk for bias, and provides no information on the quality of the exercise performance. The frequent supervised training sessions, however, seek to ensure correct execution of exercises and use of the training-log. Lastly, this study was performed prior to finalizing the RCT. Adherence was not defined as an outcome in the RCT protocol and since outcome analyses will be based on 'intention-to-treat' and not 'per protocol' this study served only as a supplement to later trial results. At the time of executing current study, we assumed that the number of included participants would be adequate to see a tendency in adherence. Nevertheless, the small sample size may explain the wide confidence intervals and the lack of statistical significance and precluded a multiple regression analysis. Other relevant factors to explore for association could be comorbidity, alcohol, smoking, socio-economic status, radiotherapy induced side-effects, disease stage, distance or travel time to hospital, motivation, and self-reported QoL.

In conclusion, our study found a high adherence to preventive swallowing exercises in HNC patients undergoing (chemo-)radiotherapy, both in home-based exercises and in supervised sessions, when compared to other studies, although median adherence to home-based exercises was below the defined 80% threshold. We acknowledge that adherence in an RCT may be higher than in the everyday clinical situation due to surveillance bias. However, we find it reassuring that HNC patients comply with a preventive swallowing program, which requires some time investment from the patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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ORCID

Sara Fredslund Hajdú  <http://orcid.org/0000-0002-2519-4337>

Irene Wessel  <http://orcid.org/0000-0001-9986-5001>

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