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ORIGINAL ARTICLE

Early preventive exercises versus usual care does not seem to reduce trismus in patients treated with radiotherapy for cancer in the oral cavity or oropharynx: A randomised clinical trial

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ABSTRACT

Purpose. In head and neck cancer patients undergoing curative radiotherapy, we investigated the benefits and harms of an early exercise regime on trismus.

Material and methods. Patients with head and neck cancer undergoing radiotherapy were centrally randomised to exercises 5–6 times for 45 minutes during and after radiotherapy supervised by a physiotherapist in addition to usual care versus usual care alone. The primary outcome was change in maximal interincisor distance (MID) measured at 5 and 12 months. Secondary outcomes were change in cervical ranges of motion, tissue tightness, and health-related quality of life. Mixed model analysis of repeated measures adjusted for tumour size and operation was conducted to assess the effect of early preventive exercises across time periods.

Results. Of the 100 patients included, two patients withdrew and one died before the onset of radiotherapy. The unadjusted mean difference in MID at 12 months after having completed radiotherapy was 0.83 mm (95% confidence interval (CI) −3.64–5.29, p = 0.71) in the exercise intervention group compared with the control group. When adjusted for operation and tumour size, the effect of the exercise intervention on mean MID from baseline to 12-month follow-up was 5.92 mm (95% CI −0.48–12.33, p = 0.07). Of the secondary outcomes, cervical rotation showed a statistically significant deterioration in the exercise group compared with the control group (p = 0.01). No significant effects were observed on the other secondary outcomes.

Conclusions. In patients with cancer in the oral cavity or oropharynx, early supervised exercises combined with self-care treatment focusing on mobility exercises to reduce trismus do not seem to provide additional beneficial effects compared with usual care during curative radiotherapy.

Background

The treatment of head and neck cancer is either surgery, radiotherapy, concomitant chemotherapy, or a combination of these modalities [1]. Combined treatment with radiotherapy and chemotherapy is highly toxic and has severe adverse effects on the function of the upper respiratory and the digestive systems. These adverse effects typically include limited mouth opening (trismus), dryness in mouth (xerostomia), difficulties with swallowing (dysphagia), chewing and talking, restricted tongue- and neck mobility, pain, and lymphoedema [2–4]. The direct effect of radiation on the medial pterygoid muscle or the masseter muscle, ultimately results in fibrosis and contracture with a gradual onset noted at about nine weeks after treatment is completed [2]. It has been estimated that between 5% and 45% of patients develops trismus after radiotherapy for head and neck cancer [3,5]. Trismus may cause poor oral hygiene, and contribute to impaired swallowing and speech [6]. Patients with

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head and neck cancer suffer from fatigue, psychosocial problems, and low health-related quality of life (HRQOL) [7].

Rehabilitation has become an important issue as both the number of patients diagnosed with head and neck cancer, and patients surviving treatment are increasing [8]. Physiotherapy is an essential part of this rehabilitation but only a few studies have been published, with poorly described interventions and outdated radiotherapy equipment [3,6,8]. Early intervention with exercises seems to have a positive effect on swallowing and maximal interincisor distance (MID) [8]. As trismus in head and neck cancer patients is difficult to treat [3], prevention is crucial. We therefore conducted a randomised clinical trial on the benefits and harms of early preventive exercises based on self-care and weekly support and guidance by a physiotherapist plus usual care versus usual care, in patients with head and neck cancer undergoing curative radiotherapy.

Material and methods

Recruitment of participants

The trial was a parallel group; two-armed superiority randomised clinical trial including patients diagnosed with cancer of the oral cavity or oropharynx undergoing radiotherapy (Figure 1). Patients were referred to the University Hospital of Copenhagen, Rigshospitalet (UCR), from the Copenhagen region, southern parts of Zealand, Lolland, Falster, Bornholm, the Faroe Islands, and Greenland.

Designated physicians and nurses of the oncology out-patient clinic at the UCR included the patients. Criteria for inclusion were: age ≥ 18 years; diagnosis of cancer of the oral cavity or oropharynx; referral to curative radiotherapy; and signed informed consent.

Exclusion criteria were: operative reconstruction of bone or skin transplant; damaged motor nervous system during surgery that affected the neck and shoulder function; diseases which could influence the symptoms of adverse events in the temporomandibular joint (TMJ) or the cervical spine (e.g. rheumatism, arthritis, neurological diseases); severe psychiatric co-morbidity (including dementia) or poor general condition, which would significantly impair participation in the trial; inability to read or understand Danish; patients referred to palliative radiotherapy; or lack of informed consent.

Eligible patients were given a patient information leaflet and oral information by a nurse, and were, after giving oral and written consent, referred to the trial from the oncology out-patient clinic.

The trial was approved by the regional Scientific Ethics Committee [journal no. (KF) 01 2006–6097] and the Danish Data Protection Agency. The trial was registered at ClinicalTrials.gov [NCT00780312] before inclusion of the first participant.

Randomisation procedure

Computer randomisation was performed by the Copenhagen Trial Unit (CTU). Randomisation was stratified according to operation prior to radiotherapy (yes, no).

Baseline assessment and follow-up

Data collection was scheduled at baseline, 1 or 2 days after onset of radiotherapy, and follow-up at 5 and 12 months after completed radiotherapy.

Outcome assessors were blinded to group allocation, and were not involved in the interventions. Patients were instructed not to reveal their group allocation to outcome assessors. Data were entered in the computer system of a person not involved in the trial, with no knowledge of the treatment allocation.

Interventions

Patients randomised to the exercise group received individual guidance and physiotherapist supervised exercises once a week for 45 minutes during the radiotherapy treatment period. The radiotherapy treatment lasted for 5–6 weeks, depending on the treatment dosage, which was 66–70 Gy, with either 5 or 6 weekly fractions. The intervention was carried out by the two study coordinators (physiotherapists N. Høgdal and K. Stage). The supervised physiotherapy sessions included the exercises and instructions in lymphedema self-drainage in the booklet.

For home training, all patients in the exercise group performed a standard programme consisting of seven exercises. Each exercise was carried out with five repetitions and should be performed five times per day. The patients in the intervention group were also instructed to use sugar free chewing gum five times a day for up to 10 minutes. Chewing gum was supplied by the physiotherapist. Two months after terminated radiotherapy, the patients were instructed in self-administered lymph drainage and exercises for the following 10 months (Supplementary Exercise booklet and Redaction of protocol, available online at http://www.rigshospitalet.dk/RHenglish/Menu/Departments+and+Clinics/Centre+of+Head+and+Orthopaedics/Department+of+Occupational+Therapy+and+Physiotherapy/Research/Early+preventive+exercises+versus+usual+care.htm).

The choice of frequent daily slow dynamic exercises, stretching exercises, chewing gum and instructions in lymphedema self-drainage was hypothesised

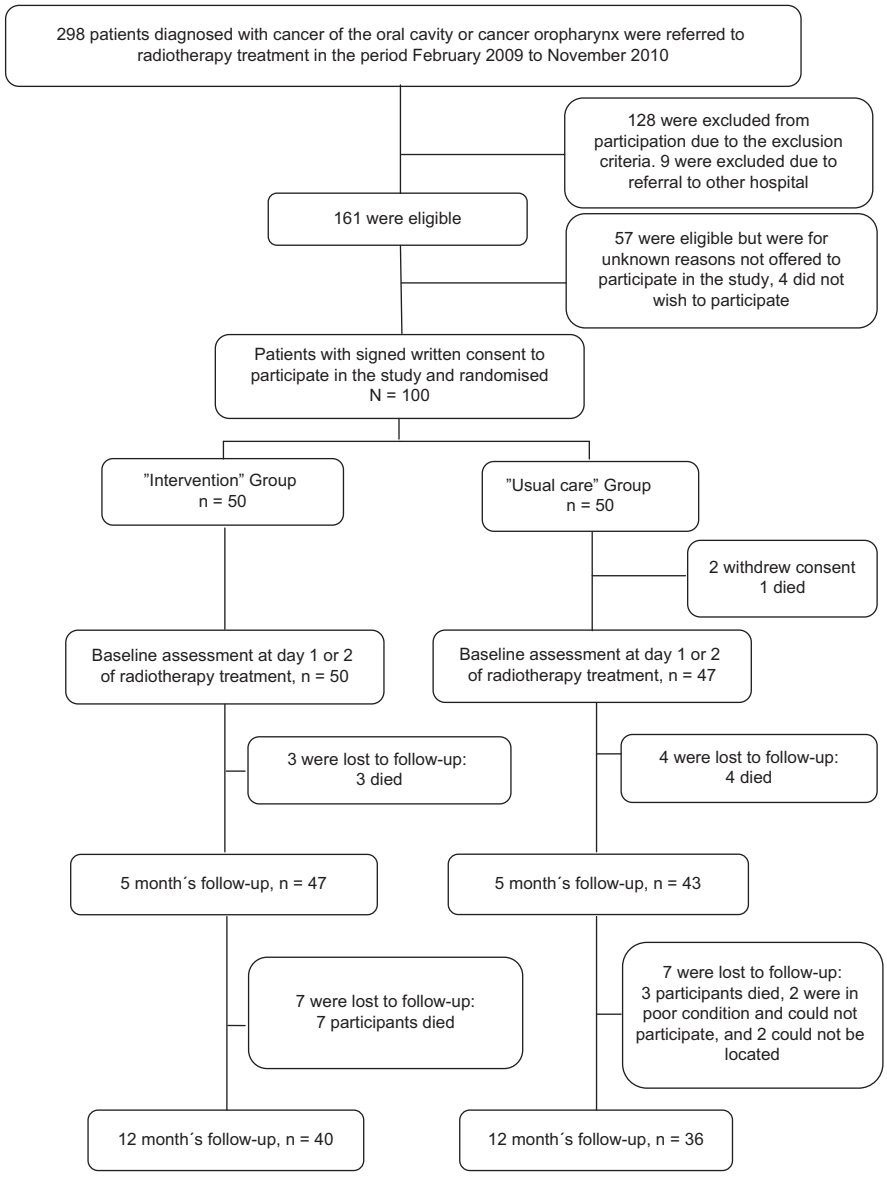

Figure 1. CONSORT diagram. Enrollment of patients and number of patients participating in baseline and follow-up assessment.

to maintain blood circulation and mobility of the muscles, joints and skin in the radiated area in order to prevent fibrosis and contracture.

Usual care consisted of treatments and advices offered by the oncologist and other healthcare providers, including instructions in mouth opening exercises by a nurse for approximately 10 minutes prior to the onset of radiotherapy.

Outcomes

Primary. The primary outcome was change in maximal vertical interincisor distance (MID) using the TheraBite Range of Motion Scale, ATOS Medical which has been used in other trials [9]. The measurement was taken between the middle of the front left upper and lower tooth. If there were no teeth, the measurement was taken between the upper and lower gum at level with frenulum labii superioris and inferioris. Trismus was defined as a MID $\leq$ 35 mm, as proposed by Dijkstra et al. [10]. Normal mouth opening was considered to be larger than 35 mm.

Secondary. Secondary outcomes were active cervical ranges of motion, measured by the Acumar Single Digital Inclinometer, Model ACU001 (Lafayette Instrument, IN, USA) attached to a helmet. Subjective tissue tightness related to opening the mouth wide was reported by means of a Likert scale. These questions were developed for the present trial, and have not been validated. HRQOL was measured by the European Organization for Research and Treatment of Cancer, generic cancer questionnaire (EORTC QLQ-C30) and specific symptoms related

to head and neck cancer by the Head & Neck cancer symptom-specific questionnaire (EORTC H&N35). The EORTC scores were transformed into a score from 0 to 100. A high function score in EORTC QLQ-C30 represented a high level of functioning. A high score in symptoms in EORTC QLQ-C30 and H&N35 represented worse symptoms. A clinically important difference was considered to be 10 units of difference [11].

Information about age, diagnoses, type of surgery, chemotherapy, and co-morbidity was attained from the hospital record forms. Patients were asked about smoking habits, alcohol intake, marital status, working status, and education. The participants were asked by the physiotherapist to what extent they performed their daily exercises, the amount of repetitions, and any reasons for not having performed the prescribed amount. This together with attendance of physiotherapy sessions were recorded weekly.

Sample size

We used a standard deviation of approximately 7 mm of mean MID reported in the literature [9]. A minimal important difference of MID was set to 5 mm. With 80% power (beta = 0.20) and a level of significance of alpha = 0.05, each intervention group should include 49 participants.

Statistical analysis

The primary outcome, difference in change in MID, was compared using a mixed model analysis of repeated measures. We conducted unadjusted analyses, analyses adjusted for the stratification variable (operation); and analyses adjusted for operation and tumour size (T1–T2 vs. T3–T4), as other studies have demonstrated an impact of tumour size on musculoskeletal structures and HRQOL in head and neck cancer patients [5,7].

The primary analyses were based on participants who completed all three assessment periods.

Furthermore, secondary analyses were performed as follows. Missing values for survivors at 5 and 12 months after completing radiotherapy were imputed using best-worst case imputation (highest value imputed in the exercise group, and lowest value in the usual care group) and worst-best case imputation (lowest value imputed in the exercise group, and highest value in the usual care group), and a similar analysis was conducted. The same approach was used to analyse the scores on the EORTC subscales. A p-value below 0.05 was chosen as statistical significant. All analyses were made using SPSS software, version 19.

Results

A total of 100 patients were equally allocated to early exercises and usual care versus usual care between February 2009 and November 2010. The two intervention groups appeared well balanced at baseline except for marital status (Table I).

Figure 1 shows the flowchart of the trial participants. Seven patients (3 in the intervention group and 4 controls) were lost to follow-up at 5 months, and 14 patients (7 in the intervention group and 7 controls) at 12 months, leaving a total of 40 participants in the intervention group and 36 in the control group at 12-month follow-up.

For the primary analysis of the intervention group only 36 persons were included, as 14 persons of the initial 50 persons did not perform a full set of data, as they did not turn up to all three assessments (due to bleeding, recurrence, poor condition and death). For the primary analysis of the usual care group only 34 persons were included, as 16 persons of the initial 50 persons did not turn up for all three assessments (due to withdrawal, recurrence, poor condition and death).

No significant differences in distribution of patients lost to follow-up between the exercise group and the usual care group were seen at 5 months ($p = 0.88$), or at 12 months ($p = 0.68$).

Primary outcome

Figure 2A shows the changes in the overall mean MID. Not all patients attended all follow-up visits, and one patient was bleeding at baseline. The unadjusted mean difference in MID at 12 month after having completed radiotherapy was 0.83 mm (95% confidence interval (CI) −3.64–5.29, $p = 0.71$) in favour of the exercise intervention group. When adjusted for the stratification variable, operation, the mean difference in MID at 12 months was 1.91 mm (95% CI −3.42–7.24, $p = 0.48$) in favour of the exercise intervention group.

When adjusted for both operation and tumour size, the effect of the exercise intervention on mean difference in MID at 12 months was 5.92 mm (95% CI −0.48–12.33, $p = 0.07$) in favour of the intervention group.

When the worst-best case imputation was conducted, the effect of exercise intervention on mean difference in MID was 4.87 mm (95% CI −1.21–10.95, $p = 0.11$), after adjustment for tumour size and operation. When the best-worst case imputation was conducted, the effect of the exercise intervention on mean difference in MID was 8.14 mm (95% CI 1.45–14.84, $p = 0.02$) after adjustment for tumour size and operation.

Table I. Baseline characteristics at entry into the trial.

Characteristic	Intervention group N = 50	Usual care group N = 47
Age, mean (SD), yr.	58.6 (8.6)	58.5 (10.7)
Female, N (%)	13 (26)	14 (30)
Comorbidity, Charlson Index*, mean (SD)	3.38 (1.4)	2.91 (0.2)
Cancer site		
Oral cavity, N (%)	8 (16)	12 (26)
Oropharynx, N (%)	42 (84)	35 (74)
Tumour size		
T3-T4, N (%)	24 (48)	15 (32)
Nodal stage		
N0, N	9	9
N+, N	41	38
Radiotherapy dose 66–70, mean (SD), Gy	67.2 (1.1)	66.8 (1.0)
5 weekly fractions, N	4	1
6 weekly fractions, N	46	46
IMRT, N	46	41
CRT, N	4	6
cCHT, N	36	30
EGFr, N	8	5
Small surgery, N	8	10
Smoker, N (%)	16 (32)	13 (28)
Alcohol intake, mean (SD) – alcohol drink/week	14.9 (18.1)	12.9 (13.5)
BMI, mean (SD) kg/m^2	25.5 (5.6)	24.3 (4.4)
Work status		
At work, N	10	7
Sick leave, N	17	18
Retired, N	23	22
Marital status		
Living together, N (%)	21 (42)	30 (64)

*Charlson Index, Comorbidity score added to age score.
cCHT, concomitant chemotherapy; CRT, conventional radiation therapy; EGFr, epidermal growth factor receptor; IMRT, intensity-modulated radiation therapy.

At 12-month follow-up, 25 patients had trismus, 14 of 40 (35%) patients in the experimental intervention group compared with 11 of 36 (31%) in the usual care group (p = 0.31).

The nodal stage had no significant impact on mean difference in MID at 12 months (p = 0.09), nor had co-morbidity (p = 0.59); smoking (p = 0.47); dose of radiotherapy (66, 68 or 70 Gy) (p = 0.51); concomitant chemotherapy (p = 0.50); or cancer in the oral cavity compared to oropharynx cancer (p = 0.63).

Secondary outcomes

Among the secondary outcomes, only cervical rotation showed a statistical significant difference in favour of the usual care group of 20.42° (95% CI −36.15–−4.69, p = 0.01), after adjustment for tumour size and operation. No significant effects were observed on the other secondary outcomes.

Additional analysis

Of the 50 patients in the experimental intervention group, 12 (24%) patients showed high adherence to the prescribed home exercises. Of these, 10 were active with work-out in the local health centre, daily walks, bicycle rides or working in the garden, and two were mainly sedentary. Of the 18 (36%) patients who showed medium adherence, two were active with daily walks, 16 were mainly sedentary. Three patients were unable to perform the prescribed mouth opening exercises due to pain, two patients due to depression, four because of infection and nine patients because of fatigue. Of the 20 (40%) patients who showed low adherence, all were mainly sedentary. Four were unable to perform the prescribed exercises due to depression, one due to high alcohol abuse, four because of infection and pain, and 11 felt too tired. Difference in mean change in MID in the high adherence group was not significantly higher than in the low adherence group (3.72 mm, 95% CI − 11.98–4.51, p = 0.77) or in the medium adherence group compared with the low adherence group (3.97 mm, 95% CI -11.84–3.9, p = 0.63) after adjustment for tumour size and operation.

The unadjusted effect of the exercise intervention on mean change in MID at 12 months in the T3/4

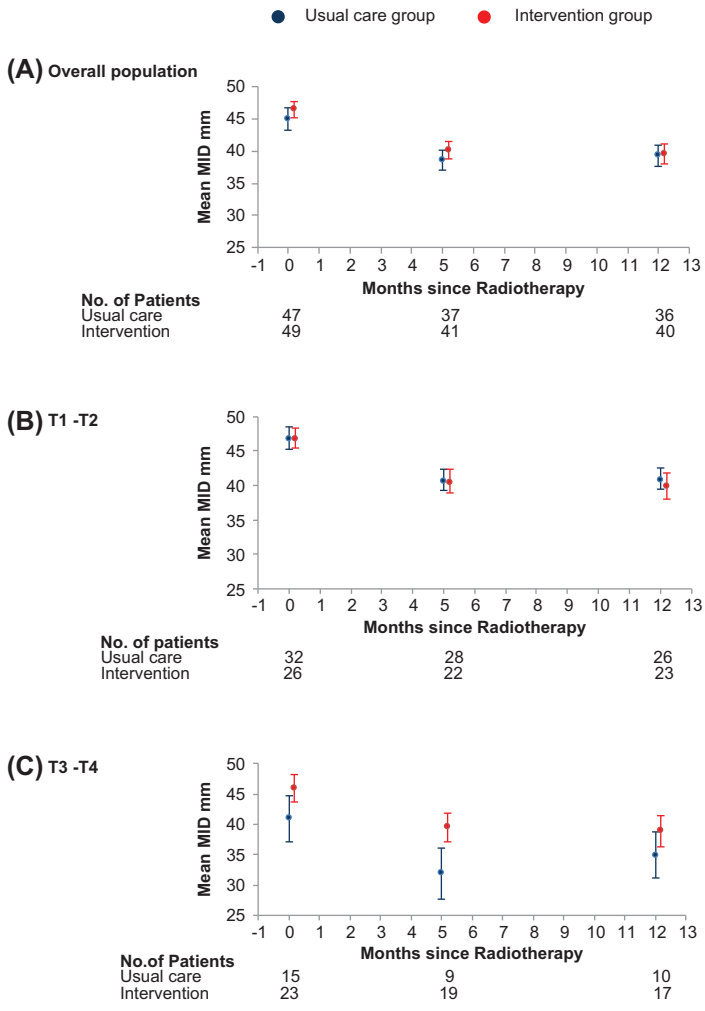

Figure 2. Mean maximal mouth opening (MID) in mm with standard error of the mean (error bars) over time according to treatment group. Measurements are shown for all patients (Panel A), those with less severe tumour size T1–T2 (Panel B) and those with more severe tumour size T3–T4 (Panel C).

group was 6.73 mm (95% CI − 4.13–17.62, p = 0.21) in favour of the intervention group.

Discussion

This randomised clinical trial showed no significant benefits of an early exercise intervention for preventing trismus following radiotherapy for head and neck cancer. The intervention did not improve HRQOL or alleviate symptoms related to head and neck cancer 5 and 12 months after treatment nor did it prevent the feeling of tissue tightness or prevent decrease in cervical range of motion. We even observed a small deterioration in the physiotherapy group regarding head rotation. No other harm related to the exercises was observed.

Our present results are in agreement with the findings of a prospective non-randomised study by Ahlberg et al. [12].

The physiotherapist sessions of our trial were hypothesised to support the home exercise programme and be feasible to implement afterwards if the trial had showed a positive effect. However, for many patients, the sessions with the physiotherapist were almost the only intervention, as they did not perform the prescribed exercises at home. Accordingly, we cannot rule out that our experimental intervention has been too light. In contrast, one could argue that the exercise programme was too heavy. Seven exercises five times daily could be too onerous for patients undergoing intense head and neck cancer treatment.

Rehabilitation based on self-care in the present form does not seem to be a promising strategy to reduce disability in the majority of patients that are treated for head and neck cancer. However, adherence with the home exercise programme was high in only 12 of the participants in the intervention group (24%). All patients in the high-adherence group

had good support from friends and spouses, which also could have added to the high adherence. A positive relation between exercise adherence and increasing MID has been described [13]. A study by Melchers et al. also showed that beside fatigue and pain due to mucositis, self-discipline, and having a clear goal are important for maintaining exercises [14]. Once patients in the latter study had reached their goal or felt there was no effect, they stopped exercising. In our trial, the goal for some patients may have seemed unclear, as reduced mouth opening develops slowly over time and most of the patients during and immediately after radiotherapy have mainly fluid nutrition combined with a feeding tube. Many of the patients may therefore not have been aware of having restricted mouth opening until they tried to eat solid food. In a study by van der Molen et al., patients were encouraged to exercise every day, but on average, patients in their study only practiced four days per week [15]. Van der Molen et al. found this adherence acceptable considering the burdensome chemo-radiotherapy. In our additional analysis, we found no significant association between low adherences to self-care and the intervention effect of mean difference in MID at 5 and 12 months.

Our trial has some strengths. Central computer randomisation and blinded assessment of the primary outcome reduce the risks of selection and detection bias [16–18]. Unadjusted and adjusted analyses were conducted, taking the stratification variable into consideration [19]. To counteract the drop in power and risks of attrition bias due to drop-outs, analyses were conducted with imputation of missing values [20–22]. The best-worst case analysis suggests that the lack of effect of the intervention could be caused by drop-outs, whereas the worst-best case analysis confirms our unimputed analysis of no statistical effect of exercises.

Our randomised clinical trial also has some limitations. First of all, the reduction due to mortality makes it impossible to draw firm conclusions as the drop-outs decrease our power. An expected drop-out of 20% was not taken in to account, due to a limited time frame of the study. Secondly, the low adherence to the self-care intervention may have reduced the effectiveness of the experimental intervention. It is, however, important to notice, that even though only a few patients were able to comply with the self-care programme, most of the patients turned up for the supervised physiotherapy sessions. In a pilot study with patients suffering from inoperable lung cancer undergoing chemotherapy, patients did not adhere to self-care but had high adherence to supervised training [23]. This suggests that future studies should be based on supervised exercises rather than on self-care. However, one could argue, that supervised exercises several times per day as recommended in order to preventing radiation-induced contracture and fibrosis are difficult or even unrealistic to provide, and other options must be found. It is also important to notice that 68% of the patients in the intervention group were mainly sedentary, and suffered from fatigue and depression. Physical activity applied to a cancer population can alleviate symptoms, such as fatigue and depression, and have a positive effect on physical function [24]. It therefore seems of interest to examine if patients with head and neck cancer would benefit from an exercise programme focusing on both prevention of trismus and dysphagia, and general physical fitness.

Abandoning testing preventive exercise interventions in this patient group is not justified by the results of this trial. Instead there is a need to find new approaches for preventive rehabilitation with the goal of maintaining swallowing function, social eating, and mobility of the jaw and neck. It is still unclear, if exercises can prevent radiation-induced fibrosis and contracture. The type and frequency of exercises to recommend is also unclear, and therefore more studies in this area are needed. We recommend that larger randomised clinical trials with supervised training or developing strategies to improve adherence concerning self-care are conducted. Screening of expected adherence to the intervention should be investigated and used for stratification in future protocols. We also recommend that randomised clinical trials with patients who are at high risk of developing trismus (e.g. patients with T3–T4 disease or with radiological evidence of invasion of the medial pterygoid muscle) should be conducted; as such patients may be more likely to respond to the intervention.

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Supplementary material available online

Supplementary Exercise booklet and Redaction of protocol, available online at http://www.rigshospitalet.dk/RHenglish/Menu/Departments+and+Clinics/Centre+of+Head+and+Orthopaedics/Department+of+Occupational+Therapy+and+Physiotherapy/Research/Early+preventive+exercises+versus+usual+care.htm)