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Feasibility of a supervised and home-based tailored exercise intervention in head and neck cancer patients during chemoradiotherapy

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Abstract

Objective: Chemoradiotherapy (CRT) for head and neck cancer (HNC) is associated with high toxicity that adversely affects physical functioning, body composition, fatigue, quality of life and treatment outcomes. Exercise interventions during treatment might counteract these negative effects. We therefore assessed the feasibility of an exercise programme for HNC patients during CRT.

Methods: Forty patients were offered a tailored 10-week endurance and resistance training with supervised and home-based sessions. Feasibility endpoints were (1) adherence (main outcome): $\geq 60\%$ attendance; (2) recruitment: $\geq 30\%$; (3) retention rate: $\geq 85\%$ and (4) compliance rate: $\geq 60\%$. Physical performance, muscle strength, body composition, quality of life and fatigue were assessed pre- and post-intervention.

Annemieke Kok and Ellen Passchier contributed equally to this manuscript.

Martijn M. Stuiver and Caroline M. Speksnijder contributed equally to this manuscript.

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Results: Overall adherence was 54%. The recruitment rate was 36%, and the retention rate was 65%. Compliance to the supervised intervention protocol was 66%. Statistically significant decreases were found in mean grip strength, fat-free mass and clinically relevant deteriorations on several domains of quality of life, and fatigue subscales were found.

Conclusion: We conclude that this exercise programme for HNC patients during CRT in its current form is feasible for only a minority of patients. We suggest adaptations to improve adherence and retention rates for a definitive multicentre trial.

Trial registration: This study is registered at the Netherlands Trial Register (NTR7305), 6 June 2018, retrospectively registered.

KEYWORDS

chemoradiotherapy, endurance training, exercise intervention, feasibility study, head and neck cancer, resistance training

1 | INTRODUCTION

Radiotherapy combined with concurrent chemotherapy (CRT) for locally advanced head and neck cancer (HNC) is associated with high toxicity with a negative impact on physical functioning, body composition, fatigue and quality of life (Bressan et al., 2016; Rogers et al., 2006; Silver et al., 2007; Taylor et al., 2004). Treatment toxicity contributes to unintentional weight loss, which is a key characteristic of malnutrition. Already at diagnosis prevalence of critical weight loss is substantial (19%) (Jager-Wittenaar et al., 2007), and may increase up to 50%, despite intensive nutritional support (Beijer et al., 2013; Jager-Wittenaar et al., 2011). Weight loss during HNC treatment is characterised by loss of lean body mass, including muscle mass (Hunter & Jolly, 2013; Jager-Wittenaar et al., 2011). Loss of muscle mass is associated with a decreased health-related quality of life (HR-QoL), physical decline, increased risk of treatment toxicity, higher complication rates, and lower survival rates in patients with HNC (Grossberg et al., 2016; Jung et al., 2019; Rogers et al., 2006; Sealy et al., 2020; Silver et al., 2007; Wendrich et al., 2017). To maintain or restore muscle mass during and after treatment, an adequate nutritional intake combined with physical exercise are prerequisites (Fearon et al., 2013). Physical exercise interventions during and after anti-cancer treatment in cancer populations positively affect fitness, fatigue, HR-QoL, and treatment completion rates (Campbell et al., 2019; Scott et al., 2018; van Waart et al., 2015). Moreover, higher levels of physical activity and fitness are associated with prolonged survival in several cancer populations (Patel et al., 2019). Most of this evidence is based on studies in patients with breast or colon cancer. Patients with HNC, however, are generally less active compared to other cancer patients: only 30.5% meet physical activity public health guidelines before diagnosis, which further decreases to 8.5% after diagnosis (Rogers et al., 2006). This sedentary behaviour can exacerbate the loss of muscle mass due to decreased muscle activity. Therefore, interventions aiming at improving physical activity and preserving muscle mass are needed. On average, compared to other

cancer patients, the HNC population is older, less educated and has a less healthy lifestyle, with higher tobacco and alcohol consumption (Hashibe et al., 2009). Moreover, there is an increase in HNC caused by human papillomavirus (HPV), with better prognosis and different patient characteristics leading to a more heterogeneous HNC group (Sabatini & Chiocca, 2020). Therefore, effects from exercise interventions in other cancer populations may not be generalizable to the HNC population. Pilot studies investigating physical exercise during (chemo)radiation in HNC are limited, have small sample sizes, and mainly focus on efficacy outcomes (e.g., physical functioning and HR-QoL) instead of feasibility outcomes (Rogers et al., 2013; Samuel et al., 2013; Zhao et al., 2016). It therefore remains unclear whether patients with HNC will be able to complete an exercise intervention to a sufficient degree for the intended effects to occur during CRT.

In a previous study on exercise preferences, only 50% of the HNC patients indicated that they felt being able to participate in an exercise programme (Rogers et al., 2009). The majority preferred to exercise alone, unsupervised, and with flexible scheduling. We therefore developed an exercise programme during CRT adjusted to these preferences, incorporating strength and endurance training at moderate intensity, in a combined supervised and home-based setting. All exercises were suitable for training at home and tailored to patients' individual capacity.

The primary aim of this study was to assess the feasibility of this tailored exercise programme for HNC patients during CRT. Our secondary aim was to assess changes from pre- to post-intervention in physical performance, muscle strength, body composition, fatigue and health related quality of life (HR-QoL).

2 | METHODS

2.1 | Participants and design

Consecutive patients with locally advanced HNC were recruited at the University Medical Center Utrecht and the Netherlands Cancer

Institute, between January 2018 and January 2020. Study inclusion criteria were (1) scheduled to receive CRT; (2) age ≥ 18 years; (3) sufficient Dutch writing and reading skills; (4) Karnofsky Performance status > 60 ; (5) able to walk ≥ 60 m without aid and (6) no contraindication for physical activity. Demographic and medical data were collected by a study-specific baseline questionnaire and chart review. Weekly dietary consultations were scheduled as part of usual care. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (17-630) and by the Institutional Review Board of the Netherlands Cancer Institute. Written informed consent was obtained from all participants.

2.2 | Exercise intervention

The exercise intervention consisted of a 10-week combined endurance and resistance training with supervised sessions as well as home-based sessions. The 10-week intervention started, preferably, the week before the start of the 7-week CRT, continued during treatment, and ended 2 to 5 weeks after CRT completion. Due to the short time frame between treatment decision and the start of treatment, the study protocol was adapted 6 weeks after start of the study, allowing baseline measurements also in the first or second week of CRT. Patients attended one session per week at the hospital, supervised by a physiotherapist (PT). Patients were instructed to perform home-based endurance exercise for 6 days a week and resistance training three times a week.

The endurance training consisted of 30 min moderate-intensity physical activity; 15 min brisk walking and another 15 min of physical activity of their own choice. Patients were instructed to use the Borg scale (6–20) to rate perceived exertion (RPE) to guide exercise intensity for the endurance training (Borg, 1982), aiming for an RPE between 12 and 15. An activity tracker, the Fitbit Zip (Fitbit LLC, San Francisco, CA), with daily step count was used to motivate patients and provide them with feedback during home-based activities. Individual targets were based on the distance achieved during the 6MWT.

For the resistance training, patients were instructed to perform six exercises three times a week, targeting major muscle groups (arms, legs, shoulders and core) using body weight and elastic bands for resistance. One of the resistance training sessions per week was performed at the hospital. Exercise type and resistance was adjusted to the participants' capacity based on pragmatic 15-RM testing and RPE range 12 to 15. Exercise intensity was increased in steps of 10% if patients exceeded the prescribed 15 repetitions. Likewise, intensity was decreased if patients were unable to complete 12 repetitions or reported worsening of symptoms due to the exercise.

2.3 | Primary outcome: Feasibility

The primary outcome of this study was the feasibility of the exercise intervention. Feasibility endpoints and accompanying success criteria were based on previous studies (Singh et al., 2018): adherence (main outcome): $\geq 60\%$ attendance to the supervised training sessions;

recruitment: $\geq 30\%$ of approached patients participating; retention rate: $\geq 85\%$ completing the intervention, and compliance: $\geq 60\%$ exercising according to the protocol. Adherence to the supervised sessions was defined as the number of attended sessions out of the 10 offered sessions and was recorded by the physiotherapist. Adherence, recruitment and retention rates were obtained by keeping a clinical research file. Compliance with supervised exercise sessions was registered by the physiotherapists, and home-based sessions were recorded by patients in an exercise log.

2.4 | Secondary outcomes

Secondary outcomes included physical performance, muscle strength, body composition, HR-QoL and fatigue. Physical performance was measured with the 6-Minute Walk Test (6-MWT) (Schmidt et al., 2013). Hand grip strength was assessed using the JAMAR dynamometer (Patterson Medical, Warrenville, IL), upper leg and arm muscle strength was assessed by using the Microfet handheld dynamometer (Hoggan scientific, Salt Lake City, UT) according to standardised procedures using the best of three trials on each side for analysis (Trutschnigg et al., 2008). Functional lower body strength was measured by the 30-Second Chair Stand Test (30-SCST) (Jones et al., 1999) (Jones et al., 1999) (Jones et al., 1999). Body composition was assessed by Bioelectrical Impedance Analysis (BIA) using the Quadscan 4000 (Bodystat Ltd, Douglas, Isle of Man) according to the standard operating procedures (Zweers et al., 2018) in a fasted state for at least 2 h. The Kyle equation was used to calculate fat-free mass (FFM) (Kyle et al., 2004). Fat-free mass index (FFMI) was derived from FFM (kg) divided by height (m) squared (kg/m^2). Baseline measurements of physical performance, muscle strength, and body composition were performed at the hospital and were re-assessed post-intervention (10 to 12 weeks post-baseline).

HR-QoL was measured using the EORTC QLQ-C30 and QLQ-H&N35 questionnaires (Aaronson et al., 1993; Bjordal et al., 1999). Fatigue was measured using the Multidimensional Fatigue Inventory (MFI) (Smets et al., 1996). Clinically important differences were defined as a change in scores of at least 10 points on the EORTC subscales and two points on MFI subscales. Questionnaires were administered on paper at baseline, midway (5 weeks post-baseline), and post-intervention (10 to 12 weeks post-baseline). Participants who dropped out were asked to provide the main reason for dropout and to complete the post-intervention assessments. Consecutive participants and non-participants were approached for an interview (until data saturation was reached) to gain insight into exercise preferences, barriers and facilitators. These qualitative data will be reported in another paper. Data was captured and stored in Castor (Amsterdam, The Netherlands), an electronic data capture system.

2.5 | Sample size calculation

The aim for our main outcome, i.e., adherence, was at least 60% with a minimal acceptable adherence of 45%. Therefore, a sample size of

37 patients (power of 80%) was needed. For compliance, the same precision applies. With 37 patients, a precision resulting in a one-sided 95% lower limit confidence interval (CI) of 17.5% (80% power) was estimated.

2.6 | Statistical analyses

Analyses were performed using IBM SPSS version 26.0 (IBM Corporation, Armonk, NY). Demographic and clinical data were reported as

proportions, mean with standard deviation, or median with interquartile range. Feasibility outcomes were described in counts and frequencies with 95% confidence intervals. Paired *t* tests were used to examine within-group changes in physical performance.

Within-group mean changes for patient reported outcomes at baseline, midway and post intervention were evaluated using linear mixed modelling with a random intercept and time as fixed factor, adjusted for centre.

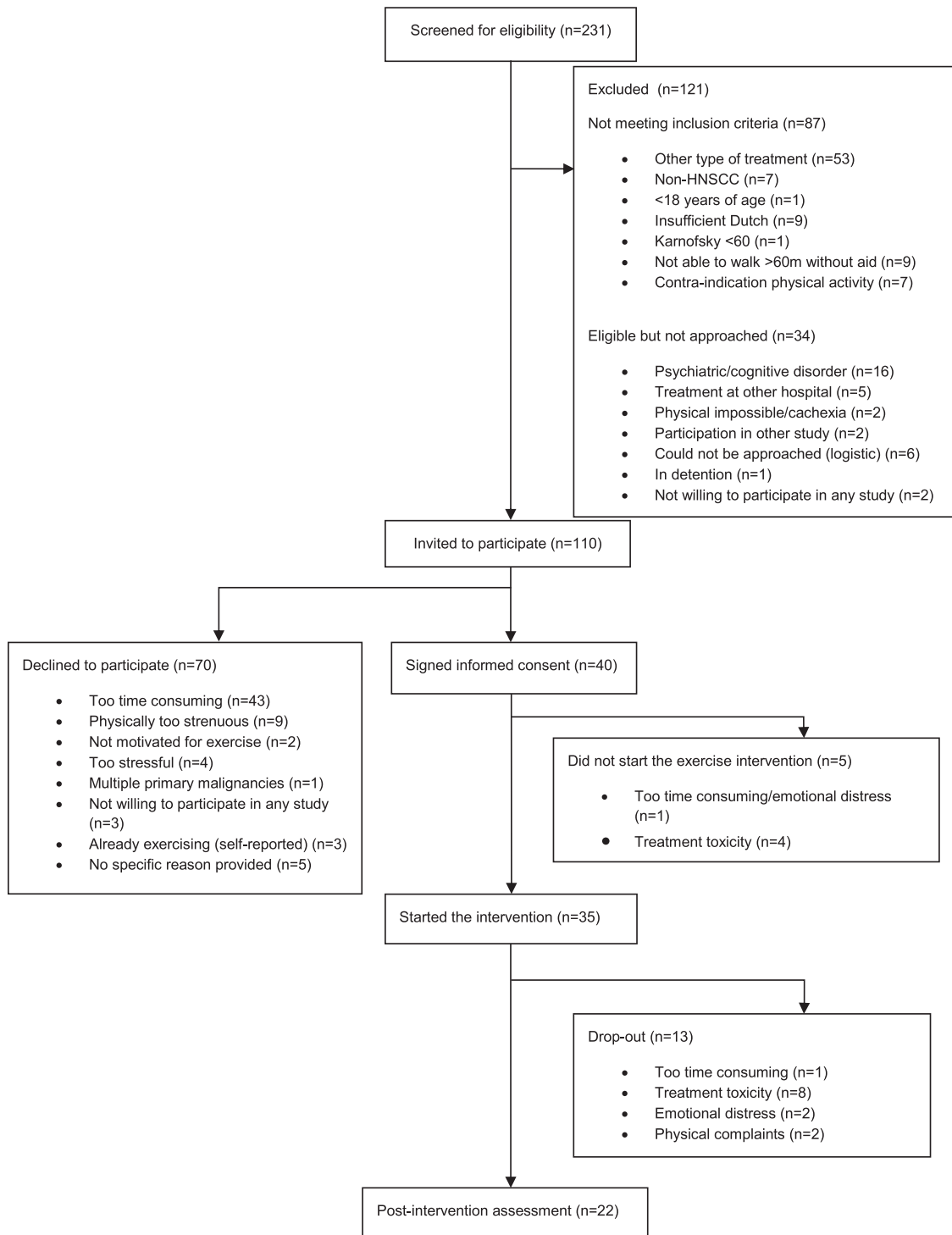


FIGURE 1 Flow chart participant recruitment and retention

3 | RESULTS

In total, 231 patients were screened for inclusion. One hundred and ten patients met the inclusion criteria and were approached for participation in the study. Of those, 40 patients (36%) signed informed consent. Five initially included patients cancelled their participation before the first session of the exercise intervention, due to treatment toxicity and/or emotional distress. Finally, 35 patients (of 110) started the intervention (Figure 1). One participant withdrew consent for using his data, leaving 34 participants for analysis. Due to the COVID-19 pandemic, recruitment had to be terminated after Participant 35 started the intervention. Patients' baseline characteristics are listed in Table 1.

3.1 | Primary outcome: Feasibility

3.1.1 | Adherence

Overall adherence to the supervised sessions for the 34 participants was 182 of 340 sessions (54%). Fifteen of the 34 participants (44%) attended at least 60% of the sessions (Figure 2). Patients who completed the intervention ($n = 22$; 63%) attended a median number of eight supervised sessions (IQR 4–9), while patients who dropped-out during intervention ($n = 13$; 37%) attended a median number of two supervised sessions (IQR 2–3). Attendance during the sessions planned after completion of cancer treatment was lower as compared to during CRT, respectively 41% versus 58% (Figure 2). Reasons for not attending or cancelling the supervised session are shown in Table 2, in which treatment toxicity was most often mentioned.

3.1.2 | Recruitment rate

Recruitment rate was 36% (95%CI: 27%–45%) and thus exceeded the feasibility criterion for recruitment (30%). The most common reason for declining participation in the study was the perception that it would be too time consuming ($n = 43$, 61%) (Figure 1). Due to a slow inclusion, the inclusion criteria were broadened in October 2018; from then also patients receiving a combination of cetuximab and radiotherapy were eligible to participate if meeting all other inclusion criteria.

3.1.3 | Retention rate

Twenty-two of the 34 (65%) participants completed the 10-week intervention period, resulting in a dropout rate of 35%. The most important reason for dropping-out was treatment toxicity ($n = 8$, 67%) (Figure 2).

3.1.4 | Compliance

Compliance with the home-based programme could not be assessed, as only three participants (9%) returned complete

TABLE 1 Demographic and clinical baseline characteristics of the participants

| Variables | Overall study population ($n = 34$) |
|---|---------------------------------------|
| Sex; n (%) | |
| Male | 27 (79.4) |
| Female | 7 (20.6) |
| Age (years); median (sd) | 58 (35–70) |
| BMI (kg/m^2); mean (sd) | 24.9 (5.4) |
| Educational level; n (%) | |
| Low | 11 (32.4) |
| Middle | 10 (29.4) |
| High | 10 (29.4) |
| Missing | 3 (8.8) |
| Marital status; n (%) | |
| Single/divorced/widowed | 11 (32.4) |
| Married/living together | 23 (67.6) |
| Employment; n (%) | |
| Paid employed | 16 (48.5) |
| Self-employed | 7 (21.2) |
| Unemployed/household/ retired | 5 (15.2) |
| Disabled for work/other | 5 (15.2) |
| Smoking status; n (%) | |
| Current | 2 (5.9) |
| Past | 22 (64.7) |
| Never | 8 (23.5) |
| Missing | 2 (5.9) |
| Alcohol consumption; n (%) | |
| Current user | 17 (50.0) |
| Stopped | 12 (35.3) |
| Never | 4 (11.8) |
| Missing | 1 (2.9) |
| Tumour location; n (%) | |
| Oral cavity | 6 (17.6) |
| Oropharynx | 17 (50.0) |
| Hypopharynx | 3 (8.8) |
| Larynx | 2 (5.9) |
| Nasopharynx | 3 (8.8) |
| Unknown primary tumour | 3 (8.8) |
| TNM stage; n (%) | |
| Stage III | 13 (38.2) |
| Stage IV | 21 (61.8) |
| HPV positive; n (%) | 15 (44.1) |
| Type of treatment | |
| CRT | 32 (94.1) |
| BRT | 2 (5.9) |
| Adjuvant CRT | 5 (14.7) |
| Comorbidities; n (%) | 11 (32.4) |

Abbreviations: BMI, body mass index; BRT, cetuximab-based bioradiotherapy; CRT, cisplatin-based chemoradiotherapy; HPV, human papilloma virus; TNM, tumour, node, metastasis classification according to the 8th edition.

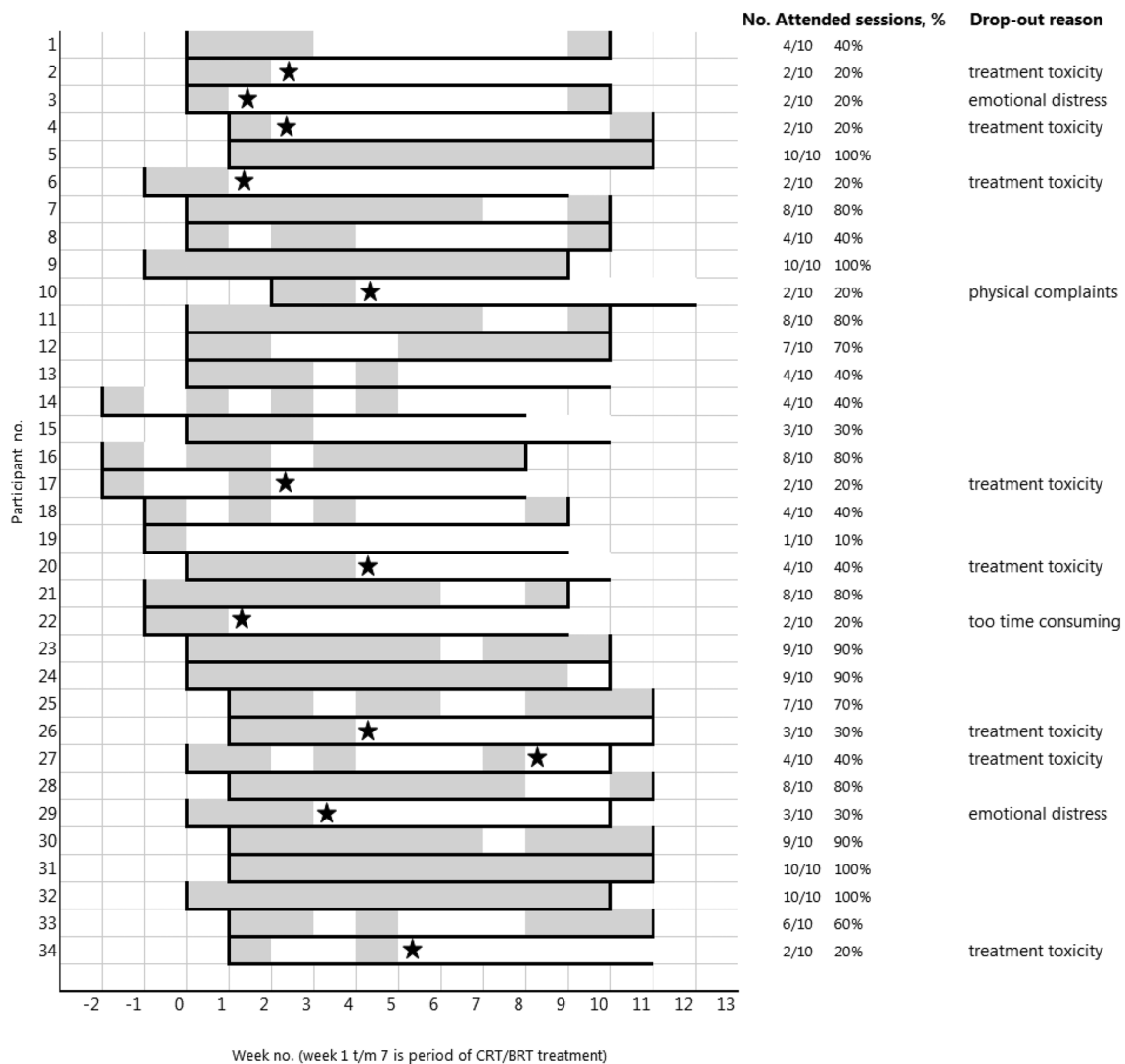


FIGURE 2 Number of attended training sessions per patient. Each grey box represents an attended session. Each white box represents a not attended session. Horizontal black lines represents the 10-week intervention period. Vertical black lines at the start and end of the intervention period represent the baseline and post-intervention measurements. Star symbols represent the timing of dropout.

exercise logs. Compliance of the supervised strength exercises, defined as an RPE range of 12 to 15 combined with ≥ 15 RM-testing, showed compliance to the protocol in 66% over the sessions attended.

3.1.5 | Adverse events

Two serious adverse events occurred. One participant was admitted to the hospital for analysis of loss of arm strength and sensation. These symptoms seemed to be related to previous surgery and were already present prior to study entry, but intensified during the intervention. The participant was able to continue to participate in the intervention without arm strength exercises. The other participant collapsed during the first training session due to

orthostatic hypotension, probably as a result of exercise in combination with chemo-induced dehydration and antihypertensive medication. After stabilisation and monitoring in the emergency unit, the participant was dismissed the next day and discontinued study participation.

3.2 | Secondary outcomes

3.2.1 | Physical performance, muscle strength and body composition

Twenty-four participants completed both the baseline and post-intervention physical performance measurements. No significant differences in physical performance and knee extension strength were

found between baseline and post-intervention measurements. Mean handgrip strength and elbow flexion strength significantly decreased during the intervention period (grip strength: -2 kg [95% CI: -4 ; 0]; elbow flexion strength: -28 N [95%CI: -43 ; -12]). Mean body weight significantly decreased from baseline to post-intervention: -5.7 kg (95%CI: -7.5 ; -3.8) of which 49% was loss of FFM: -2.8 kg (95%CI: -4.1 ; -1.6) (Table 3).

TABLE 2 Reasons for not attending a training session in the first 5 weeks and last 5 weeks of the exercise intervention of the participants who completed the 10-week exercise intervention

| Main reason for absence training session | Missed training sessions Week 1–5 (n = 24, 100%) | Missed training sessions Week 6–10 (n = 44, 100%) |
|---|--|---|
| Organisational (planning/ conflicting appointments) | 4 (16.7%) | 0 (0.0%) |
| Patient-related (planning/lack of motivation) | 2 (8.3%) | 8 (18.2%) |
| Treatment toxicity | 8 (33.3%) | 20 (45.5%) |
| Hospitalisation for chemotherapy | 2 (8.3%) | 3 (6.8%) |
| Physical complaints (not related to treatment) | 3 (12.5%) | 0 (0.0%) |
| Gastrostomy placement | 1 (4.2%) | 0 (0.0%) |
| Missing | 4 (16.7%) | 13 (29.6%) |

Abbreviation: n, the number of missed training sessions.

3.2.2 | Health related quality of life and fatigue

Results for HR-QoL are shown in Appendix S1 (Table S4). Overall, HR-QoL deteriorated during CRT (week 5 post-baseline). Some domains recovered at 12-week post-baseline, shortly after treatment, whereas scores on most symptom scales were still higher at that time, as compared to baseline.

Appendix S1 (Table S5) shows the results for fatigue. At week 5 post-baseline, patients reported clinically relevant increases on all domains, except for mental fatigue. Scores on general fatigue, physical fatigue and reduced motivation in week 12 slightly improved as compared to week 5 post-baseline.

4 | DISCUSSION

The primary aim of our study was to assess the feasibility of a tailored exercise programme with combined home-based and supervised endurance and strength sessions, for patients with HNC during CRT. To assess feasibility, we focused on adherence (main outcome), recruitment, retention and compliance rates. With an overall adherence of 54%, we did not achieve our goal of at least 60%. Recruitment rate was sufficient but the retention rate was lower than expected; 65% instead of 85%. Attendance to the supervised sessions declined after treatment completion, once the participants no longer visited the hospital for radiation treatment. Although the exercise intervention was adjusted to the participants' (changing) capacity during treatment, treatment toxicity was still the most common reason for not attending an exercise session and premature ending study participation. Protocol compliance during the supervised sessions was 66%.

In a recent review on exercise interventions in HNC patients during treatment adherence rates varied between 45% up to 94% (Bye et al., 2020). Our adherence rate of 54% was lower than our aim, and

TABLE 3 Physical performance, muscle strength and body composition at baseline and post-intervention presented in means (sd) and mean differences (95% CI)

| Variables | Baseline (n = 24) | 12 weeks after baseline (post-intervention) (n = 24) | Baseline to 12 weeks Differences | p value |
|--|-------------------|--|----------------------------------|---------|
| Physical performance | | | | |
| 6-min walking test [min] | 522 (109) | 517 (89) | -5 (-43 ; 33) | 0.79 |
| 30-sec chair stand test [n] | 15 (5) | 15 (5) | 0 (-2 ; 2) | 0.73 |
| Muscle strength | | | | |
| Hand grip strength [kg] | 42 (11) | 40 (10) | -2 (-4 ; 0) | <0.01 |
| Knee extension [N] | 289 (97) | 298 (101) | 10 (-37 ; 56) | 0.67 |
| Elbow flexion [N] | 241 (89) | 213 (77) | -28 (-43 ; -12) | <0.01 |
| Body composition | | | | |
| Body weight [kg] | 78.3 (16.2) | 72.6 (15.3) | -5.7 (-7.5 ; -3.8) | <0.01 |
| Fat-free mass [kg] | 57.1 (12.2) | 54.3 (11.6) | -2.8 (-4.1 ; -1.6) | <0.01 |
| Fat-free mass [%] | 73.5 (6.5) | 75.5 (7.0) | 2.0 (0.7 ; 3.2) | <0.01 |
| Fat-free mass index [kg/m ²] | 17.9 (2.8) | 17.0 (2.7) | -0.9 (-1.3 ; -0.5) | <0.01 |

in the lower range compared to the other studies. Especially in the period shortly after treatment a high number of sessions were missed, and we hypothesise that on-site training at the hospital does not seem to be feasible after HNC treatment completion. Probably this is due to the highest level of treatment toxicity at the end of CRT and the first weeks afterwards (Beijer et al., 2013; Driessen et al., 2016). Symptom burden of HNC treatment was also considered as a reason for non-adherence in an exploratory trial (Capozzi et al., 2016). Also, long travelling distance to the hospital and planning difficulties (patients prefer to schedule training sessions combined with medical visits, which are less frequent after treatment) were reported in our study as reasons for not attending the training sessions after treatment.

The recruitment rate of 36% exceeded the 30% we aimed for and corresponds to previous studies (Singh et al., 2018). Yet the recruitment period was twice as long as expected, even after broadening our eligibility criteria to include patients receiving cetuximab and radiotherapy due to a lower number of eligible patients. Other studies reported even higher recruitment rates of approximately 60% (Capozzi et al., 2016; Lonkvist et al., 2017). In accordance with other studies, time constraints often due to travelling time was the main reason for not being willing to participate in our study, even only one session per week was hospital-based (Sheill et al., 2019).

Almost two thirds of the 34 participants starting with the exercise intervention completed the intervention, resulting in a retention rate of 65%, which was fairly equal to the 60% reported previously (Capozzi et al., 2016). Other studies reported much higher retention rates varying between 83% and 100% (Grote et al., 2018; Rogers et al., 2013; Zhao et al., 2016). However, these studies were not completely comparable to ours. Some focused on training during radiotherapy with patients possible experiencing less toxicity as compared to CRT (Grote et al., 2018; Rogers et al., 2013). In other studies, interventions were delivered on-site during treatment and post-CRT at home with telephonic support (Rogers et al., 2013; Zhao et al., 2016). Participants preterm ending their study participation mostly stopped at or before week 5. Treatment toxicity, decreased motivation, and physical inability were the main reasons for dropout in our study.

While compliance to the home-based intervention could not be assessed, compliance to the protocol of the supervised exercises was 66%. Thus, for those attending the supervised sessions, it seems that the resistance exercises were feasible and sufficiently tailored to their personal capacities.

Two serious adverse events were reported resulting in unplanned hospital admissions. We cannot rule out that the exercise intervention contributed to these events, which both occurred during CRT. Careful monitoring of patients before and during the exercise intervention is therefore advised.

The secondary aim of our study was to assess changes in physical performance, muscle strength, body composition, HR-QoL and fatigue. We did not find significant changes in knee extension strength and physical performance. Significant decreases in grip strength and elbow flexion strength were found. Regardless of the

exercise intervention and dietary treatment, body weight and FFM significantly declined during CRT. Previous research showed weight loss during CRT for HNC was particularly loss of fat-free mass; i.e., 71% of weight loss was due to loss of FFM (Jager-Wittenaar et al., 2011). In our study, 60% of weight loss could be attributed to a loss in fat mass and only 49% to loss of FFM. Our results suggest that an exercise intervention might help to counteract loss of FFM, but only a large randomised controlled trial would allow definitive conclusions. It is important to prevent FFM loss during CRT as loss of FFM has adverse effect on treatment toxicity, tolerance and survival (Willemsen et al., 2020). Therefore, exercise interventions during treatment should preferably be combined with intensive nutritional support and monitoring.

On average, a relevant decline in HR-QoL during treatment was found, despite the exercise intervention. Fatigue scores increased from baseline to week 5 and remained stable until week 12. A randomised pilot study (Grote et al., 2018) showed a 9% increase in general fatigue during treatment for the intervention group and a 40% increase for the control group, suggesting a positive effect of exercise on cancer-related fatigue for cachectic patients with HNC during radiotherapy, as was also shown for other cancer types (Cramp & Byron-Daniel, 2012). Due to our small study sample and the lack of a control group, we cannot draw conclusions about whether our exercise intervention led to less deterioration of HR-QoL and less increase in fatigue than would have been the case without the intervention.

4.1 | Strengths and limitations

With 34 participants at two study sites, this is one of the largest pilot studies assessing the feasibility of a tailored exercise intervention in HNC during CRT with combined supervised and home-based sessions. With this sample size, we were able to report feasibility outcomes with sufficient power. However, we also have to consider limitations of our study. Firstly, participants of our study are likely to already be more active than non-participants, which might have resulted in selection bias. This can be inferred from the baseline results of the 6MWT, which show higher scores as compared to comparable HNC populations (Samuel et al., 2013; Zhao et al., 2016). Also, compared to data from the Dutch Head and Neck audit, participants in our study are younger, and the prevalence of HPV is high (44.1%) (van Overveld et al., 2018). Lastly, the lack of a control group makes it difficult to attribute changes in physical capacity, performance, HR-QoL, and fatigue between baseline and post-intervention to the exercise intervention. However, these preliminary data can be used for sample size calculations for future large-scale interventions.

4.2 | Recommendations for future exercise trials in HNC

This feasibility study revealed several barriers that could be addressed to increase inclusion and adherence. Lowering the study load for

participants (e.g., less travel, improved logistics planning and fewer questionnaires), using activity trackers that automatically record and store data and give immediate feedback might increase adherence, recruitment and completeness of data collection. To offer a more tailored exercise intervention and to improve feasibility, understanding of patients' preferences to determine preferable timing, intensity and setting is needed.

Some recommend to engage patients with a training programme before treatment but start the actual training programme after treatment (Capozzi et al., 2016; Lonbro et al., 2013). This might result in higher retention and recruitment rates. We suggest to adapt the training schedule in weeks 6 to 10 by replacing on-site supervised training by home-based sessions with remote support, to account for the increasing treatment toxicity. After treatment, patients with HNC prefer training at a community location (Jackson et al., 2018). In other cancer patient populations home based training sessions combined with supervised sessions by a physiotherapist resulted in higher adherence rates and showed positive effects on fatigue, cardiorespiratory fitness and muscle strength (van Waart et al., 2015; Velthuis et al., 2010). Training at a community location will be more convenient for our patient population and diminish travel time. The benefits of training in group classes should also be further explored as one study showed that patients with HNC preferred exercise alone prior to participating in an exercise trial, but afterwards preferred group classes which increased motivation for some participants (Jackson et al., 2018). This also emphasises the need for tailored exercise interventions: participants should be able to choose between home-based, on-site, alone or group classes. Furthermore, careful focus on the personal goals and capacity of 'hard to engage' patients and addressing knowledge gaps about benefits of physical activity and their perceived barriers might increase recruitment and adherence rate (Chinn et al., 2006). Analysis of our qualitative data will give insight into exercise preferences, and possible barriers and facilitators from patients' perspective.

We conclude that this intensive exercise training during CRT for patients with HNC is feasible for a minority of patients in its current form. Adherence to the supervised exercise sessions was lower than expected, although the recruitment rate, retention rate and compliance rate during supervised sessions were reasonably good. We suggest adaptations to improve adherence and retention rates. A more personalised approach, including better motivators and immediate feedback by activity trackers, needs further investigation prior to conducting a definitive multicentre trial.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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