Phase III randomised trial

Progressive resistance training rebuilds lean body mass in head and neck cancer patients after radiotherapy – Results from the randomized DAHANCA 25B trial

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A B S T R A C T

Purpose: The critical weight loss observed in head and neck squamous cell carcinoma (HNSCC) patients following radiotherapy is mainly due to loss of lean body mass. This is associated with decreases in muscle strength, functional performance and Quality of Life (QoL). The present study investigated the effect of progressive resistance training (PRT) on lean body mass, muscle strength and functional performance in HNSCC patients following radiotherapy.

Patients and methods: Following radiotherapy HNSCC patients were randomized into two groups: Early Exercise (EE, n = 20) initiated 12 weeks of PRT followed by 12 weeks of self-chosen physical activity. Delayed Exercise (DE, n = 21) initiated 12 weeks of self-chosen physical activity followed by 12 weeks of PRT. Lean body mass, muscle strength, functional performance and QoL were evaluated at baseline and after week 12 and 24.

Results: In the first 12 weeks lean body mass increased by 4.3% in EE after PRT and in the last 12 weeks by 4.2% in DE after PRT. These increases were significantly larger than the changes after self-chosen physical activity (p < 0.005). Regardless of PRT start-up time, the odds ratio of increasing lean body mass by more than 4% after PRT was 6.26 (p < 0.05). PRT significantly increased muscle strength, whereas functional performance increased significantly more than after self-chosen physical activity only after delayed onset of PRT. Overall QoL improved significantly more in EE than DE from baseline to week 12.

Conclusion: PRT effectively increased lean body mass and muscle strength in HNSCC patients following radiotherapy, irrespective of early or delayed start-up.

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Head and neck squamous cell carcinoma patients (HNSCC) treated with radiotherapy typically experience a weight loss of 6–12% of pre-treatment body weight [1,2]. The weight loss is caused by the cancer disease itself and by the side effects of radiotherapy, such as mucositis and dysphagia impeding sufficient energy intake. This weight loss is reported to persist more than two years post-treatment [3,4]. It has been shown that weight loss negatively impacts survival, morbidity, functional performance and quality of life (QoL) in HNSCC patients [5,6].

More than 70% of the weight loss in HNSCC patients is reported to be lean body mass [11], which is associated with impaired muscle strength, a decline in physical activity, functional capacity and decreased independence in performing activities of daily living [1,7]. Consequently, effective interventions to regain lean body mass, muscle strength and functional performance in radiotherapy treated HNSCC patients are strongly needed.

Progressive resistance training (PRT) increases muscle mass, muscle strength and functional performance in healthy individuals including elderly sarcopenic individuals [8,9]. Randomized controlled trials on the general effects of PRT in cancer survivors are limited and predominantly involve breast- and prostate cancer survivors [10]. Moreover, only few studies primarily in breast cancer survivors have investigated PRT-induced changes in lean body mass [11].

Prolonged side effects and sustained negative energy balance following radiotherapy [12] may inhibit the potential effect of PRT on lean body mass in HNSCC patients. Both impaired physical performance reducing sufficient training effort and chronic negative net protein balance could reduce the PRT response and allow-
The present study was a multi-center, randomized, stratified and parallel-grouped study. Approval was achieved from the regional Ethics Committee for the Central Denmark Region (id: 20110065), and the study was registered at clinicaltrials.gov (identifier: NCT01509430). Eligible participants fulfilled the following inclusion criteria:

1. Histologically diagnosed with squamous cell carcinoma of the larynx (except glottic stage I + II), pharynx, oral cavity or in lymph nodes from an unknown primary tumor (stage I-IV, TNM, 2002); 2. no current or previous malignancies, psychological, social or geographical conditions that could prevent participation and training; 3. no excessive alcohol intake; 4. WHO performance status 0–1; 5. age ≥18 years; 6. completed curative radiotherapy ± chemotherapy; 7. complete tumor regression after treatment; and 8. written consent.

All 41 patients received accelerated radiotherapy according to DAHANCA guidelines (www.dahanca.dk) with IMRT if relevant to total tumor dose of 66–68 Gy, 6 fractions/week, and total dose of 50 Gy to the elective neck volume. In thirty-three patients, radiotherapy was combined with the hypoxic cell sensitiser nimorazole (1200 mg/m²), and 22 patients received weekly concomitant cisplatin (40 mg/m²). Nine patients received the EGFr-antibody Zalutumumab. No elective neck dissection was performed except for those previously had neck dissection.

At the two months post treatment follow-up, patients were given oral and written information about participation before signing a written consent. Before randomization patients were stratified according to HPV/p16 status (positive vs. negative), relative weight loss (cut-off: 8.5% of pre-treatment body weight) and presence vs. no presence of feeding tube at the two months follow-up. Patients were randomly allocated to the Early Exercise (EE) or Delayed Exercise (DE) group. During the initial 12 week period, EE patients initiated 12 weeks of PRT. DE patients were not offered any organized training in this period but allowed to participate in any limitless self-chosen physical activity and thus acting as controls. In the last 12 week period patients in DE performed a PRT protocol identical to the protocol in EE, while patients in EE were encouraged to continue a self-chosen PRT regime, but chose level and type of physical activity themselves.

Progressive resistance training

Progressive resistance training

At different commercial training facilities located close to the patients’ residences thirty PRT sessions were evenly dispersed over 12 weeks. Patients performed 2–3 sets of 8–15 repetition maximum of seven conventional exercises: leg press, knee extension, hamstring curls, chest press, sit ups, back extensions, and lateral pull down. Patients received professional instruction during two to three initial sessions in the first two weeks. Apart from approximately five occasional supervisions, all subsequent training sessions were unsupervised. Patient training logs provided information on PRT adherence. The PRT protocol has been described in detail elsewhere [2].

Assessment of primary and secondary endpoints

All endpoints were evaluated at baseline and following 12 weeks and 24 and evaluation were standardized between the involved sites. Observers involved in assessment of the primary endpoint were blinded regarding group assignment of patients. The primary endpoint was whole body lean body mass evaluated using Dual Energy X-ray Absorptiometry (DEXA) with narrow fan beam technology. DEXA is widely used to assess lean body mass and body composition and is validated in cancer patients [15]. The mean coefficient of variance of whole body lean body mass was 0.4% for both the Aarhus site (duplicate scans of three individuals) and Odense (duplicate scans of 11 individuals) site. Maximal knee extensor (KE) and flexor (KF) strength were determined using isokinetic dynamometry [16]. Maximal isokinetic (60° per sec) KE and KF and isometric KE (70° knee joint angle) and KF (20° knee joint angle) strength were determined as peak torque (Newton-meters). Isokinetic dynamometry is routinely used to assess maximal muscle strength in elderly individuals including various groups of patients [17–19]. Functional performance was evaluated by 10 m maximal gait speed; 30 s maximal chair rise; maximal stair climbing; 30 s maximal arm curls. These tests have previously been used in various patient groups including cancer [17,20]. QoL was evaluated using the EORTC QLQ-C30 questionnaire, which has previously been used in exercise studies in cancer survivors [21] and validated in Danish HNSCC patients [22]. See Supplementary material, endpoint evaluation for further details.

Statistical analysis

The study was planned to include 40 patients randomized equally into two groups. This number was based on a priori power calculation where PRT-induced lean body mass change was considered the primary endpoint. Using an expected 5% lean body mass change [2] (±5% standard deviation) with an anticipated drop-out rate of 20%, power was 0.8 and level of significance was 0.05.

All continuous data followed a normal distribution (tested using box plots, q–q-plots, histograms and dot-plots). Multivariate analyses of variance were used to evaluate possible time and group interactions of all endpoints. In case of detecting group-time interactions or time effects within groups, Student’s paired t-test evaluated changes over time within group and Student’s unpaired t-tests evaluated group differences. The effect of PRT on lean body mass was also presented as odds ratios of the relative odds of increasing lean body mass above the population median. Data from the EORTC QLQ-C30 questionnaires were assumed to be normally distributed. Thus, unpaired Wilcoxon–Mann–Whitney tests were performed to analyze group differences and the paired Wilcoxon signed rank test.
was used to analyze changes over time within groups. All completers were included in the statistical analyses. Thus, patients who did not undergo evaluation after baseline \((n=5)\) were excluded from the statistical analyses, whereas patients who dropped out between week 12 and 24 evaluation \((n=2)\) were excluded in the analyses of changes in this period. All endpoints were tested statistically using a 5% level of significance. Unless otherwise stated, data are presented as mean values ± SD. All statistical analyses were performed using STATA version 11.2 (StataCorp LP, Texas, US).

Results

Of 191 eligible HNSCC patients from July 2011 to July 2012, 41 were included for randomization providing a recruitment rate of 22% (Fig. 1). Twenty patients were allocated into EE and 21 patients into DE.

Patient inclusion/exclusion flow is presented in Fig. 1. Two patients were excluded from all physical tests because of knee injuries hindering maximal effort contractions at 12 and 24 weeks. Baseline characteristics for both groups of all randomized patients and separately on non-completers are presented in Table 1 showing that both groups were balanced at baseline. The overall PRT adherence of both groups was 95% and no adverse events were reported.

Lean body mass

After the first 12 weeks lean body mass increased by 4.3% (2.3 kg; \(p<0.001\); 95% CI 1.7; 3.0) in EE after PRT, which was 1.5 ± 0.5 kg larger (\(p=0.005\); 95% CI 0.5; 2.5) than the 1.5% change in DE after self-chosen physical activity. After the last 12 weeks, lean body mass increased by 4.2% (2.4 kg; \(p<0.001\); 95% CI 1.1; 3.1) in DE after PRT, which was 2.1 ± 0.5 kg larger (\(p<0.001\); 95% CI 1.1; 3.1) than the 0.5% change in EE after self-chosen physical activity (Fig. 2 and Supplementary Table 1).

In the present population the overall 12 week increase in lean body mass irrespective of time and PRT completion was 4%. Over the first 12 weeks, the odds ratio (OR) of increasing lean body mass by more than 4% was 5.57 (95% CI 1.30; 23.93) in patients that completed PRT. Over the last 12 weeks the OR was 7.44 (95% CI 1.25; 44.19) in patients completing PRT. Overall the OR for increasing lean body mass by more than 4% in any of the two 12 week periods was 6.26 (95% CI 2.02; 19.13) for PRT versus self-chosen physical activity. The stratification factors (HPV/p16 positive patients, patients with feeding tube at the two month post-treatment follow-up or patients with a treatment-induced weight loss above 8.5%) were not significantly related to the lean body mass increase (Fig. 3).

Maximal muscle strength

After the first 12 weeks isometric KE increased by 20% (33Nm; \(p<0.001\); 95% CI 16; 50) in EE after PRT, which was 22 ± 9Nm more (95% CI 3; 42Nm, \(p=0.025\)) compared with DE after self-chosen physical activity. After the last 12 weeks isometric KE increased by 21% (34Nm; \(p<0.001\); 95% CI 17; 50) in DE after PRT, which was 32 ± 10Nm more (95% CI 12; 54Nm; \(p=0.003\)) compared with EE after self-chosen physical activity. Similar results were observed for isokinetic KF. However, a significant larger increase in isometric KF and isokinetic KE following PRT was not observed in the initial
Table 1
Baseline patient characteristics of randomized all patients and non-completers. BMI: body mass index; weight loss: loss of body weight following treatment. Unless stated otherwise values are presented as the absolute and relative number of patients and mean ± SD. * Stage III–IV includes patients with unknown primary tumor/neck node.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Early exercise (randomized patients)</th>
<th>Early exercise (non-completers)</th>
<th>Delayed exercise (randomized patients)</th>
<th>Delayed exercise (non-completers)</th>
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<tr>
<td>Number of patients</td>
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<td>6</td>
</tr>
<tr>
<td>Center</td>
<td>Aarhus</td>
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<td>13 (62%)</td>
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<td></td>
<td>Odense</td>
<td>7 (35%)</td>
<td>8 (38%)</td>
<td>0 (0%)</td>
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<tr>
<td>Age in years (range)</td>
<td>55 ± 7 (33–65)</td>
<td>52</td>
<td>58 ± 7 (41–71)</td>
<td>59 ± 5 (52–64)</td>
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<td>Body weight in kg at time of inclusion</td>
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<td>64.5</td>
<td>73.9 ± 9.6</td>
<td>65.3 ± 8.2</td>
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<tr>
<td>BMI</td>
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<td>23.6 ± 3.0</td>
<td>22.3 ± 3.5</td>
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<tr>
<td>Weight loss in kg (range)</td>
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<td>7.1</td>
<td>7.4 ± 5.0 (1.2–16.1)</td>
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<td>&lt;8.5%</td>
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<td>11 (52%)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

Fig. 2. Changes in primary and secondary endpoints from baseline to week 12 and from week 12 to week 24 in Early Exercise (EE) and Delayed Exercise (DE). Values are presented as means ± SD. # denotes significant group differences (p < 0.05), ** (p < 0.001) and (*) (p < 0.05) denote time effect within group. See Table 2 for specific p-values and 95% CI. KE: knee extension. KF: Knee flexion. PA: Physical Activity. See Supplementary Material for absolute values, specific p-values and 95% CI.
12 weeks in EE (Fig. 2), although such an effect was present from week 12 to week 24 in DE. See Supplementary Table 1 for details.

**Functional performance and quality of life**

After the first 12 weeks the increases in all functional performance tests in EE after PRT were not different compared to the increases in DE after self-chosen physical activity. After the last 12 weeks DE improved chair rise and arm curl performance significantly more after PRT than EE after self-chosen physical activity (Fig. 2 and Supplementary Table 1). After PRT in the first 12 weeks EE improved overall QoL (Global Health) and Cognitive Function significantly more than DE after self-chosen physical activity and over the last 12 weeks DE improved Physical Function significantly more after PRT than EE after self-chosen physical activity (Supplementary Tables 1 and 2).

Overall, from baseline to week 24, the primary and secondary endpoints improved within both intervention groups and no group differences were observed during this period (Supplementary Table 1).

**Discussion**

The primary finding of this trial is that 12 weeks of locally based PRT with a low level of supervision leads to a lean body mass increase in HNSCC patients following radiotherapy. Both early and delayed training groups increased their lean body mass by 4.2–4.3% during 12 weeks of PRT, which was significantly larger than the change following self-chosen physical activity (Fig. 2 and Supplementary Table 1). After PRT in the first 12 weeks EE improved overall QoL (Global Health) and Cognitive Function significantly more than DE after self-chosen physical activity and over the last 12 weeks DE improved Physical Function significantly more after PRT than EE after self-chosen physical activity (Supplementary Tables 1 and 2).

Overall, from baseline to week 24, the primary and secondary endpoints improved within both intervention groups and no group differences were observed during this period (Supplementary Table 1).

Despite inducing significant increases in all functional performance tests from baseline to week 12, PRT had no superior effect compared to self-chosen physical activity. This suggests that resuming to more normal levels of daily physical activities such as walking, cycling and different types of domestic activities has an equal positive effects when functional performance is as low receiving either dietary supplementation or placebo. Interestingly, the lean body mass increase observed in the present study exceeds the 1.3–1.5 kg increase observed in weight losing cancer patients following 113 days of administration of selective androgen receptor modulator [23] and proposes that training intervention may be more effective than medical treatment on lean body mass.

Rogers et al. [13] found no lean body mass change following 12 weeks of PRT. In that study patients initiated the first six weeks of exercise band type training at the start-up of radiotherapy at the clinic and completed the last six weeks in their own home. The small sample size and low training adherence may have influenced the results. In a group of HNSCC patients similar to the one studied in the present study, Jäger-Wittenaar et al. [24] reported a radiotherapy-induced lean body mass decrease by 4.6% and total lean body mass remained low from one to four months post-treatment despite a decrease in the prevalence of malnutrition in the study. Assuming that the reported magnitude of the lean body mass loss is representative for the patients of the present study, 12 weeks of PRT seems to almost entirely reverse the lean body mass loss in HNSCC patients.

The observed changes in maximal muscle strength clearly suggest a specific effect on maximal muscle strength regardless of PRT start-up time. In EE PRT induced significant increases in maximal isometric KE and isokinetic KF strength larger than the change following self-chosen PA in DE from baseline to week 12. However, there was no significant difference between EE and DE in isokinetic KE and isometric KF in this period. From week 12 to week 24 all measures of maximal muscle strength increased significantly more in DE than EE. The findings of non-significant group differences in two of four maximal muscle strength tests from baseline to week 12 may question the superior effect of PRT, although most likely caused by the substantial within-group variance observed in both groups. Nonetheless, the mean increases in EE were consistently greater in all maximal muscle strength tests.
as observed at baseline. All functional tests reflected tasks of common daily activities and are affected by other factors than maximal muscle strength, such as increased participation and performance in residential everyday activities of the patients, which may explain the increase in DE from baseline to week 12. From week 12 to week 24 we observed a significant larger increase in three of four functional performance tests in DE. This indicates that increasing functional performance after reaching a certain level was only effective by means of PRT, further suggesting that the increase in maximal muscle strength induced in DE in this period lead to further improvements in functional performance. Despite these differences, the overall increase from baseline to week 24 was identical between groups in all functional performance tests (Supplementary Table 1) why favoring one start-up time over the other is not substantiated.

Interestingly, QoL increased following PRT from baseline to week 12, where two measures of QoL (Global Health and Cognitive Function) increased to a greater extent in EE than in DE. Thus, participation in 12 weeks of organized PRT could improve self-perceived QoL as reported using other exercise interventions in cancer survivors [25]. However, baseline scores of the two specific measures were significantly lower in EE, strongly suggesting a larger improvement potential in this group.

As discussed previously [2], the logistic advantages minimally supervised and locally based PRT may facilitate the implementation of this training modality in the future training of HNSCC patients. Further strengths of the present study are the reliable assessment of muscle strength by means of PRT on both primary and secondary endpoints. We recognize the risk of selection bias including that the weakest patients might refuse to participate or are not included due to co-morbidity or other conditions that could inhibit training completion. Furthermore, the dimensions of the statistical analyses were based on the primary endpoint only. Thus, we acknowledge the issue of multiple testing when interpreting results from the analyses on secondary endpoints.

In summary, we conclude that 12 weeks of progressive resistance training leads to significant increases in lean body mass and that the time of PRT start-up following radiotherapy does not influence the effect. Furthermore, most measures of maximal muscle strength were significantly increased by PRT. When a certain threshold level of functional performance was achieved, PRT may have a potentially larger effect than self-chosen physical activity.

Conflicts of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.07.002.

References