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ORIGINAL RESEARCH

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Physical rehabilitation in patients with head and neck cancer: Impact on health-related quality of life and suitability of a post-treatment program

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Abstract

Objective: Physical rehabilitation programs hold the potential to mitigate deterioration in health-related quality of life (HRQoL) in patients with head and neck cancer. The objective was to assess development in relevant domains of HRQoL following a physical exercise and nutrition intervention administrated during or after treatment.

Methods: In a pilot study, 41 patients were randomized to resistance training and oral nutritional supplements during (EN-DUR, n = 20) or after (EN-AF, n = 21) radiotherapy. Global health status/QoL (GHS) and physical functioning (PF) were measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire at baseline, week 6, and week 14. Differences between the groups were assessed by analysis of covariance. A difference of ≥10 points in GHS and PF was interpreted as clinically relevant.

Results: No statistically significant differences were detected between the groups; however, clinically relevant changes and differences in GHS and PF were observed. From baseline to week 6, GHS decreased 9 points in the EN-DUR group and 23 points

in the EN-AF group and PF decreased 13 points and 21 points, respectively. From week 6 to week 14, GHS increased 14 points in the EN-DUR group and 26 points EN-AF group and PF did not change (0 points) in the EN-DUR group and increased 16 points in the EN-AF group.

Conclusion: The findings from the present pilot study are promising and indicate that a physical rehabilitation program may have a positive impact on HRQoL during treatment and enhance recovery after treatment. A definitive randomized trial is warranted.

Level of Evidence: 1b—Individual randomized controlled trial.

KEYWORDS

head and neck cancer, health-related quality of life, nutritional support, physical rehabilitation, resistance training

1 | INTRODUCTION

Patients with head and neck cancer (HNC) are faced with specific challenges and needs due to the complex treatment involving changes to critical structures for speaking, eating, and breathing in addition to facial and neck disfigurement.[1,2] This may have a significant impact on function and body image that negatively affects health-related quality of life (HRQoL) and survivorship.[3,4]

Numerous observational studies have reported HRQoL throughout treatment and recovery in patients with HNC, demonstrating that symptoms such as pain, dry mouth, and sticky saliva increase steadily during the course of radiotherapy (+/− chemotherapy) while physical functioning (PF) and global health status/QoL decrease.[5-13] The patients report maximum symptom burden and minimum functioning at the end of and immediately after radiotherapy.[4,7,11] The post-treatment period is normally characterized by gradual recovery and improvement; however, only global health status/QoL seems to reach pretreatment levels within 1 year after treatment completion.[11,13,14] Thus, the following year(s) of HNC survivorship is characterized by persistent treatment-related side effects accompanied by deteriorated functional status.[15]

Rehabilitation programs that include physical exercise and/or nutrition interventions hold the potential to mitigate some of the side effects and counteract the reduced functioning experienced by patients with HNC.[16,17] Although generally small in sample sizes and hampered by study design not tailored to study, several physical exercise intervention studies have indicated a beneficial impact of resistance training on PF, fatigue, and global health status/QoL during and immediately after tumor directed treatment.[18-21] The results from nutrition intervention studies are somewhat mixed, but two randomized controlled trials (RCTs) have demonstrated less deterioration in PF and global health status/QoL in patients receiving dietary counseling and/or oral nutritional supplements (ONS) during and after treatment.[22,23] However, to the best of our knowledge, no study has reported short- and long-term HRQoL following an intervention combining physical exercise and nutritional support in patients with HNC.[24]

On this background, we conducted a randomized pilot study in 2015 to 2016 to evaluate the feasibility and compare the impact of a new rehabilitation program during radiotherapy (EN-DUR) consisting of resistance training and ONS to a program after radiotherapy as part of an existing cancer rehabilitation program in the specialist health care in Norway. Previously we have reported data on feasibility and short-term effects on lean-body mass and body weight.[25] Eighteen of 20 patients completed the EN-DUR and 11 of 21 the EN-AF intervention. The EN-DUR intervention demonstrated high exercise-adherence (81%) and moderate ONS-adherence (57%), and a beneficial impact on lean body mass was indicated. The exercise and ONS adherence rates for the patients attending the EN-AF intervention were even higher (94% and 76%, respectively). This raises several questions related to patient needs as well as timing and setting of rehabilitation services. Subgroup analyses of attenders and nonattenders may therefore provide valuable information regarding possible factors associated with needs and utilization of rehabilitation services in patients with HNC.

The objective of the present study was to assess short- and long-term differences in HRQoL between the physical rehabilitation program administrated during vs after tumor directed treatment and describe within-group changes in HRQoL during the first year after diagnosis of HNC. Due to the low attendance-rate to the program after treatment, differences in HRQoL and sociodemographic and clinical characteristics between the attenders and nonattenders were explored.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

Patients were recruited in the period between March 2015 and March 2016 from the Clinic of Ear-Nose-Throat, Eye and Maxillofacial Surgery (ENT-clinic) at St. Olavs Hospital, Trondheim University Hospital in Norway. The patients were eligible if the following inclusion criteria were met: (a) a diagnosis of squamous cell carcinoma originated in the head and neck (naso, oro, or hypo pharynx, larynx and oral cavity, except from

stage T1N0M0 laryngeal cancer), (b) referred for curative radiotherapy with or without chemotherapy, (c) 18 to 85 years of age, and (d) able to complete baseline assessments prior to start of radiotherapy.

The study was designed as a randomized pilot study and the patients were allocated to an exercise and nutrition intervention during radiotherapy (EN-DUR) or after radiotherapy (EN-AF). The EN-DUR intervention was conducted from start to end of radiotherapy (6 weeks) at an outpatient training facility within the hospital area and consisted of 12 resistance training sessions (maximum 30 minutes per session). In addition, all patients received a booklet with nutritional advice specifically designed for patients with HNC and were provided with minimum one unit (200 mL) of ONS on weekdays (E+ by Tine SA, Norway, 350 kcal and 15 g protein per unit). On training days, the patients were asked to take one extra unit after the session. The EN-AF intervention started 2 to 4 weeks after the end of radiotherapy and was conducted at a rehabilitation clinic as part of an established 3-week cancer program. The program consisted of nine resistance training sessions (maximum 40 minutes per session), daily intake of ONS similar to the EN-DUR intervention and dietary counseling once a week provided by a dietitian. A detailed description of the interventions has been published previously.[25]

2.2 | Background variables

Sociodemographic data (age, sex, marital status, living situation, education, employment, and smoking status), nutritional status, and self-reported physical activity were obtained by a questionnaire prior to start of radiotherapy (baseline), and clinical data (diagnosis date, type and stage, recurrence, type of treatment, and comorbidities) were obtained from the patients' medical journals. Karnofsky performance status (KPS) was scored by the involved physiotherapist (J.A.S.).[26]

Nutritional status was measured by the short form of the Patient-Generated Subjective Global Assessment (PG-SGA), and a total score was summarized ranging from 0 (no problem) to 36 (severe problems) based on the recommended use of the instrument.[27-31] Self-reported physical activity level was measured by the Nord-Trøndelag Health Study Physical Activity Questionnaire (HUNT PA-Q) with a total score calculated based on the product of frequency, duration, and intensity, ranging from 0 (no physical activity) to 15 (vigorous physical activity for more than 1 hour almost every day).[32-34] Functional exercise capacity was measured by the field exercise test Modified Shuttle Walk Test (MSWT), and functional muscle strength was measured by the 30 seconds sit to stand test.[35-37]

2.3 | Outcome variables

The patients completed HRQoL questionnaires at baseline, at the end of radiotherapy (week 6), at 2 months follow-up (week 14), and 1 year later (1 year). HRQoL was measured by the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30, version 3.0) and the HNC module EORTC QLQ-H&N35.[38,39] The EORTC QLQ-C30 consists of five functional scales, three symptom scales, a global health status/QoL scale, and six single items. Global health status and PF was considered relevant C30 scales in the present study. The EORTC QLQ-H&N35 consists of seven multi-item symptom scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality, and six single-item symptom scales assessing side effects related to problems with teeth, opening mouth, dry mouth, sticky saliva and coughing, and the feeling of being ill. In addition, the questionnaire consists of five optional single-item scales (ie, questions 31-35) assessing the use of pain killers, nutritional supplements, and feeding tube and weight loss and gain. Pain, dry mouth and sticky saliva were considered relevant H&N35 scales. Scoring for the C30 and H&N35 questionnaires was conducted according to the EORTC QLQ-C30 scoring manual recommendations and range from 0 to 100.[40] A high score for global health status/QoL and PF represents high HRQoL/high functioning and a high score for a symptom scale represents a high level of symptoms/problems.

2.4 | Statistical analyses

Descriptive statistics with confidence intervals (95% CI) was the focus of the analyses due to the pilot design of the study. Distributions of the included variables were checked for normality by inspection of histograms, Q-Q-plots and tests of normality, and presented as mean with SD if approximately normally distributed or median with interquartile range (IQR) if skewed. Differences between the groups were assessed by analysis of covariance (ANCOVA) at week 6, week 14, and 1 year with the respective baseline-scores as covariate. Within-group changes were assessed by paired sample *t* tests. A difference in HRQoL scores of 10 points or more was considered clinically relevant.[41] All statistical analyses were performed using the IBM SPSS Statistics 22.0 software (IBM Corporation, Armonk, New York). *P* values < .05 were considered statistically significant.

2.5 | Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK midt 2013/2098), and the study was registered at ClinicalTrials.gov prior to study start (Identifier: NCT02439892). All patients provided written informed consent before entering the study.

3 | RESULTS

The study sample consisted of 41 patients (25 male) with an average age of 63.2 years (SD = 9.3 years). Median time from diagnosis to baseline assessment was 14 days (IQR = 11 days) and 80% had a KPS score of ≥90 at baseline. Twenty patients were randomized to the EN-DUR intervention and 21 patients to the EN-AF intervention. Characteristics of the randomized groups and attendance, attrition, and adherence rates have been presented previously.[25] At baseline,

the mean global health status/QoL and PF scores were 61 and 83 points in the EN-DUR group compared to 67 and 91 points in the EN-AF group, and the mean symptom scores of pain, dry mouth, and sticky saliva were 29, 23, and 38 points in the EN-DUR group compared to 23, 19, and 21 points in the EN-AF group. The number of complete EORTC QLQ-C30 and H&N35 forms in the EN-DUR and EN-AF groups is presented in Table 1. From baseline to 1-year follow-up, respectively, four patients died in the EN-DUR group and two in the EN-AF-group.

3.1 | Changes in HRQoL

The ANCOVA-analysis did not demonstrate any statistically significant differences between the EN-DUR and EN-AF groups in global health status/QoL, PF, or symptoms of pain, dry mouth and sticky saliva. Figure 1 presents the mean scores in global health status/QoL and PF in the two groups at baseline, week 6, week 14, and 1 year, based on the number of complete questionnaires as presented in Table 1.

However, clinically relevant changes in HRQoL from start to end of the study were observed within the EN-DUR and EN-AF groups as well as clinically relevant differences in change between the groups. From baseline to week 6, global health status/QoL decreased 9 points (95% CI: −20.6, −3.1) in the EN-DUR group compared to 23 points (−34.0, −12.5) in the EN-AF group, and PF decreased 13 points (−22.3, −3.0) compared to 21 points (−33.7, −9.0). From week 6 to week 14, global health status/QoL increased 14 points (0.9, 27.6) in the EN-DUR group compared to 26 points (7.4, 43.6) in the EN-AF group, while PF did not change in the EN-DUR group (0 points, −6.8, 7.4) compared to an increase of 16 points (4.8, 26.6) in the ENAF group. Symptoms of pain, dry mouth, and sticky saliva increased in both groups from baseline to week 6 and decreased in both groups from week 6 to week 14 (see Table 2 for the respective scores).

TABLE 1 The number of completed EORTC QLQ-C30 and H&N35 forms at each assessment point

	Baseline	Week 6	Week 14	1 year
EN-DUR group (n = 20)	20	19	18	15
EN-AF group (n = 21)	21	19	18	18

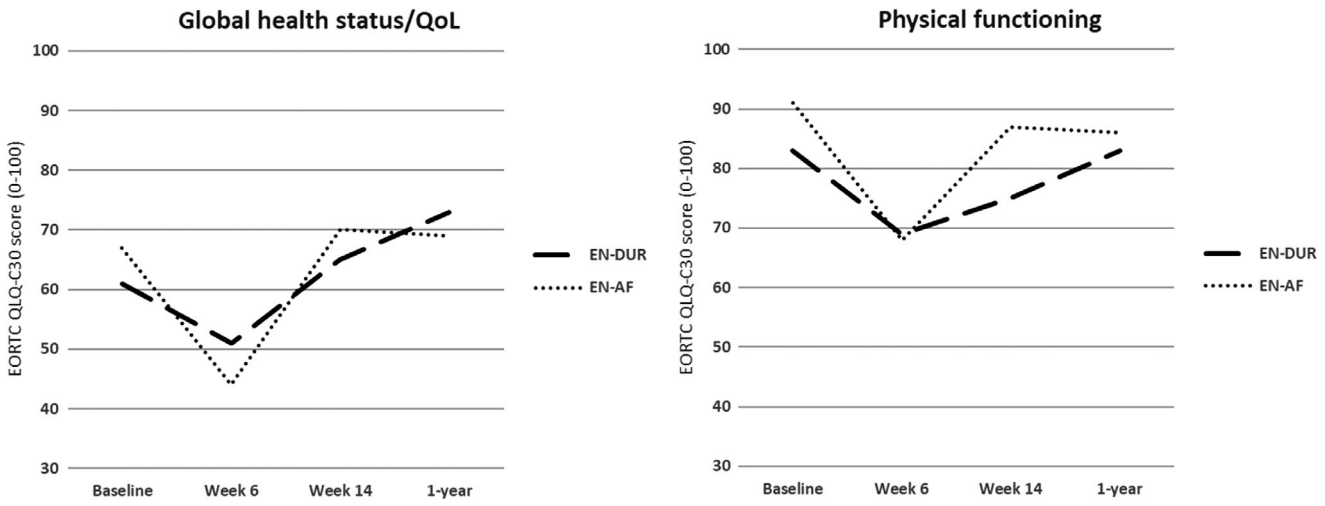

FIGURE 1 Mean scores in global health status/QoL and physical functioning in the EN-DUR and EN-AF groups at baseline, week 6, week 14, and 1 year. QoL, quality of life

TABLE 2 Mean symptom scores at baseline and week 6 and at week 6 and week 14 for the EN-DUR and EN-AF groups, respectively

	EN-DUR			EN-AF			EN-DUR			EN-AF		
	Baseline	Week 6	Diff. (95% CI)	Baseline	Week 6	Diff. (95% CI)	Week 6	Week 14	Diff. (95% CI)	Week 6	Week 14	Diff. (95% CI)
Pain	30	53	23 (11.6, 34.9)	24	52	28 (17.1, 39.7)	52	34	−18 (−27.8, −7.5)	53	22	−31 (−40.6, −21.9)
Dry mouth	24	77	53 (33.1, 72.2)	19	77	58 (42.9, 72.9)	76	74	−2 (−13.2, 9.3)	79	61	−18 (−33.8, −1.5)
Sticky saliva	39	84	45 (23.4, 67.8)	21	84	63 (46.3, 80.0	82	61	−21 (−41.6, −1.5)	86	55	−31 (−44.2, −18.6)

Abbreviation: Diff., difference of mean scores.

From baseline to 1-year follow-up, global health status/QoL increased 11 points (0.8, 21.4) in the EN-DUR group compared to reaching baseline level in the EN-AF group (0 points, −11.9, 11.9) and PF reached baseline values in the EN-DUR group (0 points, −11.9, 11.9) compared to a decrease of 7 points (−13.9, −0.7) in the EN-AF group. Symptoms of pain decreased 13 points (−27.7, 1.0) in the EN-DUR group compared to an increase of 1 point (−12.7, 14.6) in the EN-AF group. Dry mouth and sticky saliva increased 36 points

TABLE 3 Baseline characteristics of the attenders and nonattenders to the EN-AF intervention

	Attenders n = 11	**Nonattenders n = 10**	
Age; years (median, IQR)	61 (11)	67.5 (15)	
Sex			
Women	5	6	
BMI, kg/m^2 (mean, SD)	25.7 (5.0)	27.8 (9.0)	
Marital status			
Married/cohabitant	8	7	
Single/widow	3	3	
Education			
Primary or secondary school	9	7	
College/university	2	3	
Employment			
Employed	6	3	
Retired	3	7	
Disability benefits	2	0	
Smoking status			
Current smoker	0	1	
Past smoker	7	6	
Never smoked	4	3	
Karnofsky performance status			
Score ≥ 90	9	9	
Tumor site			
Pharynx	9	1	
Larynx	0	2	
Oral cavity	2	2	
Salivary gland/nasal cavity	0	5	
Planned treatment			
Concurrent chemoradiotherapy	8	2	
Radiotherapy	3	8	
	Mean (SD)	**Mean (SD)**	**Diff.**[a] (95% CI)
HRQoL			
Global health status/QoL	62.1 (22.8)	72.5 (21.9)	10.4 (−30.8, 10.1)
Physical functioning	89.1 (20.7)	92.5 (16.8)	3.4 (−20.7, 13.9)
Pain	29.5 (25.4)	15.8 (24.7)	13.7 (−9.2, 36.6)
Dry mouth	18.2 (17.4)	20.0 (23.3)	−1.8 (−20.5, 16.9)
Sticky saliva	21.2 (34.2)	20.0 (23.3)	1.2 (−25.8, 28.2)
Nutritional status	2.4 (3.4)	3.5 (5.6)	1.1 (−5.3, 3.1)
Physical activity level	2.7 (2.7)	1.8 (1.7)	0.9 (−1.2, 3.0)
Functional capacity (m)	683 (228)	504 (154)	179 (−5, 362)
Muscle strength (reps)	15 (4)	14 (3)	1 (−2, 4)

Abbreviations: BMI, body mass index; Diff., difference in mean scores; HRQoL, health-related quality of life; IQR, interquartile range; reps, repetitions.
[a]Difference in mean scores.

(22.6, 48.5) and 9 points (−16.7, 34.5) in the EN-DUR group compared to 46 points (26.5, 66.1) and 20 points (−1.0, 41.7) in the EN-AF group.

3.2 | Attenders vs nonattenders to the EN-AF intervention

Only 11 of the 21 patients (52%) randomized to the EN-AF intervention attended the program. Table 3 presents the background characteristics of the attenders and nonattenders to the EN-AF intervention before the start of treatment (baseline). The median age of the attenders to the EN-AF intervention was 61 years (IQR = 11 years) compared to 67.5 years (IQR = 15 years) among the nonattenders, and body mass index of the attenders was 25.7 kg/m^2 (SD = 5.0) compared to 27.8 kg/m^2 (SD = 9.0) among the nonattenders. More of the attenders were diagnosed with pharyngeal cancer compared to the nonattenders (n = 9 vs n = 1), and more of the attenders were scheduled for chemotherapy in addition to radiotherapy (n = 8 vs n = 2).

The attenders reported clinically relevant lower global health status/QoL compared to the nonattenders (62 vs 73 points) and more symptoms of pain (30 vs 16 points). Furthermore, the attenders reported a clinically relevant higher level of physical activity (2.7 vs 1.8 points) and had a higher functional capacity compared to the nonattenders (683 vs 504 m). No clinically relevant differences in PF, dry mouth, sticky saliva, nutritional status, or muscle strength were detected between the attenders and nonattenders.

4 | DISCUSSION

The overall aim of the present pilot study was to assess differences and describe within-group changes in HRQoL following two physical rehabilitation programs administered during or after radiotherapy (+/− chemotherapy). Due to the pilot design of the study (n = 41) with the inherent lack of power to detect statistically significant differences between groups, the main focus was to perform descriptive analyses to explore changes in HRQoL over time. Clinically relevant changes in global health status/QoL and PF were observed in both groups, with differences in change in favor of the active interventions both during and after treatment. Only half of the patients attended the intervention after treatment. Analysis of the attenders and nonattenders indicates that the two subgroups represent different populations. The attenders to the program administered after treatment reported clinically relevant lower global health status/QoL and more pain compared with the nonattenders. In addition, the attenders were younger, and more were diagnosed with pharyngeal cancer and scheduled for concurrent chemoradiotherapy than the nonattenders.

To our knowledge, this is the first intervention study that explores the development in HRQoL following a rehabilitation program administered during or after radiotherapy (+/− chemotherapy) consisting of a combination of resistance training and ONS in patients with HNC. Rogers et al conducted a randomized pilot study (n = 15) to assess the feasibility and preliminary effects of a 12-week resistance training program initiated at start of radiotherapy in patients with HNC, and reported similar findings as in the present study with less decline in overall well-being (FACT-General) and HNC specific well-being (FACT H&N) compared to standard care from baseline to week 6.[19] However contrary to our findings, the intervention group reported less increase in overall and HNC specific well-being compared to the control group from week 6 to week 12. Capozzi et al published an exploratory RCT (n = 60) in 2016 that evaluated the timing and effects of a 12-week lifestyle intervention with resistance training and health education initiated during vs after radiotherapy.[42] HRQoL was included as a secondary outcome, with a total symptom score and overall HRQoL measured before and after the interventions. In line with our results, no statistically significant differences were detected between the interventions in total symptom score or overall HRQoL, probably due to lack of power. However, contrary to our findings, no clinically relevant differences in mean scores were observed between the groups from start to end of the intervention initiated at start of treatment.[42] Another single-armed (n = 12) exercise trial by Lønkvist et al showed deterioration in most functional scales in EORTC QLQC-30 during treatment, but only minor deterioration was reported in PF.[43]

The findings in the present study confirm earlier findings from numerous observational studies that global health status/QoL and PF decrease during radiotherapy (+/− chemotherapy) while symptoms of pain, dry mouth, and sticky saliva increase steadily, and that the post-treatment period normally is characterized by gradual recovery and improvement in HRQoL and less reported symptoms.[5-13] However, an interesting and novel finding in our study is that the patients receiving the active intervention during radiotherapy (EN-DUR) experience clinically relevant less decline in global health status/QoL and PF from start to end of treatment compared with the patients receiving standard care. A similar trend was observed in the active intervention after treatment (EN-AF), with clinically relevant larger improvements in global health status/QoL and PF from week 6 to week 14 compared to the "controls" (EN-DUR). The results indicate that an intervention with resistance training and ONS either during or after radiotherapy may have positive impact on self-reported health status/QoL and PF, and justifies the implementation of a full scale RCT to investigate whether exercise and nutrition interventions lead to statistically significant improvements. To optimize adherence and retention, we suggest starting the intervention already at the time of diagnosis and extending throughout the treatment period and into the acute post-treatment phase compared to usual care. In addition, utilizing facilities close to where the patients live seems a sensible strategy to optimize retention especially in the post-treatment phase. A next-step study would profit from patient codesign on these issues.

The future RCT should probably include a combination of physical exercise and nutritional support initiated before start of tumor directed treatment with continuation during treatment and into the post-treatment recovery phase compared to a usual care group. To our knowledge, the largest RCT that has investigated the effectiveness of a physical exercise program in patients with HNC undergoing chemoradiotherapy was recently published by Samuel et al, and

conclude that physical exercise during treatment has the potential to enhance HRQoL.[44] They studied the effect of an 11-week program with aerobic and resistance training exercises on quality of life (using the generic Short Form-36), functional capacity, and worsening of fatigue. Compared with the control group, there was a statistically significant difference in favor of the exercise group on all outcomes from start to end of the intervention. Both the mental and the physical quality of life score was maintained from baseline to immediately after treatment in the exercise group compared to a significant reduction in the control group.[44] These are exciting results from a full-scale trial supporting the findings in this article, although not directly comparable due to differences especially in content of interventions and measurement instruments.

To gain more insight into possible factors associated with the utilization and needs of rehabilitation within this population, background characteristics were compared between the attenders and nonattenders to the program administrated after treatment. A clear difference at baseline was that most of the attenders (8 of 11 patients) were scheduled for concurrent chemoradiotherapy compared with only two of the 10 nonattenders. Receiving chemotherapy concurrently with radiotherapy is associated with increased symptoms of mucositis, nausea, vomiting, and fatigue compared with only radiotherapy.[45] Thus, an increase in symptoms could be expected among the attenders at the end of treatment. The younger age among the attenders may explain the higher level of self-reported physical activity and the superior functional capacity compared to the nonattenders before treatment start. However, younger cancer patients often express an increased need for rehabilitation compared to older patients, and the utilization of cancer rehabilitation services has been found to be significantly higher in younger age groups.[46-48] One of the reasons for this is suggested to be related to a greater self-perceived loss of functioning among younger patients. The latter and the aspect of still being within working age may have influenced the choice to attend the post-treatment program in the present study, possibly to regain physical and work-related functioning. In addition, the setting of the program (ie, a rehabilitation clinic located 150 km from the hospital) may have affected the decision to decline participation, and the need for more local services needs to be addressed. As a further preparation for the definitive RCT, we will map out any existing outpatient and community-based rehabilitation services within the current geographical area and, based on the findings, consider the need to design and implement new locally based interventions.

4.1 | Strengths and limitations

The present data were obtained from a relatively small single-center pilot study (n = 41) with no predefined clinically relevant difference or power and sample size calculations. Statistically significant differences between the interventions (EN-DUR and EN-AF) were neither the aim nor expected in this feasibility study; thus, we wanted to explore and compare absolute mean scores even in the absence of formal statistical significance. The two interventions administrated during and after tumor directed treatment respectively were not directly comparable due to differences in content, duration, and setting, and the reason for designing two different interventions was based on the current standards of post-treatment rehabilitation programs in Norway and the need for testing new interventions during treatment. The utilized data in the analysis of the attenders and nonattenders were obtained from only one of the two intervention arms in the pilot trial (ie, the post-treatment intervention), which implies a small number of patients (n = 21) split into smaller subgroups of attenders (n = 11) and nonattenders (n = 10).

5 | CONCLUSION

No statistically significant differences in HRQoL between the physical rehabilitation programs were demonstrated, but interesting findings of importance for designing a full-scale RCT were observed. The findings indicate that a physical rehabilitation program may have a positive impact on relevant HRQoL domains during treatment and enhance recovery after treatment in patients with HNC. In addition, the present findings also indicate an increased need for post-treatment rehabilitation among patients receiving concurrent chemoradiotherapy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception or design of the work: S.K., J.-Å.L., and L.O.; Data collection: J.A.S., T.R.B., and A.B.; Data analysis and interpretation: J.A.S., E.S., and L.O.; Drafting the article: J.A.S., A.B., T.S.S., and L.O.; Critical revision of the article: A.B., T.S.S., T.R.B., L.T., E.S., S.K., J.-Å.L., and L.O.; Final approval of the version to be published: J.A.S., A.B., T.S.S., T.R.B., L.T., E.S., S.K., J.-Å.L., and L.O.

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