Physical Activity Levels in Locally Advanced Rectal Cancer Patients Following Neoadjuvant Chemoradiotherapy and An Exercise Training Programme Before Surgery: A Pilot Study

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ABSTRACT

Background: The aim of this pilot study was to measure changes in physical activity levels (PAL) variables, as well as sleep duration and efficiency in people with locally advanced rectal cancer (1) before and after neoadjuvant chemoradiotherapy (CRT) and (2) after participating in a preoperative 6-week in-hospital exercise training programme, following neoadjuvant CRT prior to major surgery, compared to a usual care control group.

Methods: We prospectively studied 39 consecutive participants (27 males). All participants completed standardised neoadjuvant CRT: 23 undertook a 6-week in-hospital exercise training programme following neoadjuvant CRT. These were compared to 16 contemporaneous non-randomised participants (usual care control group). All participants underwent a continuous 72 h period of PA monitoring by Sensewear biaxial accelerometer at baseline, immediately following neoadjuvant CRT (week 0), and at week 6 (following the exercise training programme).

Results: Of 39 recruited participants, 23 out of 23 (exercise) and 10 out of 16 (usual care control) completed the study. In all participants (n=33), there was a significant reduction from baseline (pre-CRT) to week 0 (post-CRT) in daily step-count: Median (IQR) 4966 (4435) vs. 3044 (3265); $p<0.0001$, active energy expenditure (EE) (kcal): 264 (471) vs. 154 (164); $p=0.003$, and metabolic equivalent (MET) (1.3 (0.6) vs. 1.2 (0.3); $p=0.010$). There was a significant improvement in sleep efficiency (%) between week 0 and week 6 in the exercise group compared to the usual care control group (80 (13) vs. 78 (15) compared to (69 ((24) vs. 76 (20); $P=0.022$), as well as in sleep duration and lying down time ($p<0.05$) while those in active EE (kcal) (152 (154) vs. 434 (658) compared to (244 (198) vs. 392 (701) or in MET (1.3 (0.4) vs. 1.5 (0.5) compared to (1.1 (0.2) vs. 1.5 (0.5) were also of importance but did not reach statistical significance ($p>0.05$).An apparent improvement in daily step-count and overall PAL in the exercise group was not statistically significant.

Conclusions: PAL variables, daily step-count, EE and MET significantly reduced following neoadjuvant CRT in all participants. A 6-week pre-operative in-hospital exercise-training programme improved sleep efficiency, sleep duration and lying down time when compared to participants receiving usual-care.

Clinical trial registration: NCT: 01325909

KEYWORDS: Rectal cancer, neoadjuvant cancer treatment, physical activity, exercise, prehabilitation, surgery

Background

Cancer treatment reduces physical fitness, which appears to be worse in those receiving surgery and radiotherapy in combination with chemotherapy than in those receiving radiotherapy or surgery alone [1]. Changes in fitness are clinically important: neoadjuvant chemo- and chemoradio-therapy reduce physical fitness, objectively measured using cardiopulmonary exercise testing (CPET), which is associated with increased in-hospital morbidity following advanced rectal cancer resection [2] and decreased 1-year overall survival following upper gastrointestinal cancer resection [3].

Physical fitness is closely connected with physical activity (PA), although relationships of cause and effect are complex. Remaining physically active during and after cancer treatment improves cancer-related fatigue, psychological distress, quality of life, as well as overall survival and reduces the probability of cancer recurrence [4]. Increasing PA following cancer diagnosis may reduce the risk of cancer-specific death in people with breast and non-metastatic colorectal cancer [5-6] or death from any cause in non-metastatic colorectal cancer [6]. Exercise training during chemotherapy has a significant beneficial effect on tumour progression and chemotherapy efficacy in solid tumours [7].

For people diagnosed with locally advanced rectal cancer [Tumour, Node, Metastasis (TNM) stage >T3N+ magnetic resonance imaging (MRI) identified circumferential resection margin threatened cancer], the standard treatment is neoadjuvant chemoradiotherapy (CRT) followed by surgery [8-9]. The aim of this pilot study was to measure changes in daily PAL in people with locally advanced rectal cancer scheduled to undergo neoadjuvant CRT followed by surgical resection with a curative intent. We aimed to evaluate changes in daily step-count and overall PAL pre- and post- neoadjuvant CRT in all participants in an attempt to quantify the impact of neoadjuvant CRT on PAL. We also aimed to evaluate changes in daily step-count (number of steps taken) and overall PAL at the start and end of a pre-operative 6-week in-

hospital exercise training programme, commenced after completion of neoadjuvant CRT, comparing changes with those observed in a usual care control group (no formal exercise intervention). Exploratory aims included observing changes in other PAL variables such as: total (EE for daily-living) and active EE (PA-induced EE)PA duration; lying down time; sleep duration and efficiency; and metabolic equivalent (MET) (intensity of PA) in all participants following neoadjuvant CRT and compare changes in the exercise group compared to the usual care control group.

Methods

Participants and study design

This prospective pilot, non-randomised, parallel group, interventional controlled trial was a nested study of a clinical trial [10]. This pilot study was approved by the North West Liverpool East Research and Ethics Committee (11/H1002/12) and registered with clinicaltrials.gov (NCT01325909). Written informed consent was obtained from all participants. We recruited consecutive participants between March 2011 and February 2014 referred to the Colorectal Multi-Disciplinary Team, aged ≥18 year, with locally advanced (MRI-defined) circumferential resection margin threatened, operable rectal cancer, undergoing standardised neoadjuvant CRT with no distant metastasis and with WHO performance status <2 [11] (categorised between 0 (fully active) to 4 (completely disabled, cannot carry out self-care: totally confined to bed or chair). Exclusion criteria were: inability to give informed consent; non-resectable disease; inability to perform CPET or bicycle exercise due to lower limb dysfunction; and participants who declined surgery or neoadjuvant CRT or who received non-standard neoadjuvant CRT. After completing neoadjuvant CRT, participants were allocated to the exercise training group by default. If unable to commit to the exercise schedule (or living >15 miles from the hospital), they were asked to act as contemporaneously-recruited controls (no formal exercise intervention) with the same PA monitoring follow-up. Participant characteristics such as age; gender; past medical history; ASA score (the ASA score is a subjective assessment of patients overall health, categorised into 5 classes: I (healthy fit patient) to V (patient who is not expected to live 24 hours without surgery); and WHO status were collected at baseline visit.

All participants underwent a continuous 72 h period of PA monitoring using Sensewear biaxial accelerometer (Figure 1). PAL was measured during weekdays at baseline (2 weeks before neoadjuvant CRT), immediately following neoadjuvant CRT (week 0) and at week 3 and week 6. Participants in the exercise training group undertook a 6-week supervised in-hospital

exercise training programme (3 sessions per week). The exercise training intensities were responsive to each individual CPET at week 0 and week 3 (informed and altered according to measured work rates at oxygen uptake at lactate threshold and at peak exercise). Exercise training consisted of 40 min (including 5 min warm-up and 5 min cool-down) of interval training on an electromagnetically braked cycle ergometer (Optibike Ergoline GmbH, Germany). The interval-training programme consisted of alternating moderate (80% of work rate at oxygen uptake at lactate threshold – 4 by 3 min intervals) to severe (50% of the difference in work rates between oxygen uptake at peak and lactate threshold- 4 by 2 min intervals) intensities (total 20 min) for the first two sessions. This was then increased to 40 min (6×3 min intervals at moderate intensity and 6×2 min intervals at severe intensity). The exercise training protocol and procedures are described elsewhere [10].

TNM staging involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen, and pelvis computer-aided tomography (CT), and 1.5 T pelvic magnetic resonance imaging (MRI). All participants underwent 5 weeks neoadjuvant CRT. Standardised radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a 3D conformal technique with CT guidance. Oral capecitabine (825 mg m^{-2}) was given twice daily on radiotherapy days. No participants received brachytherapy. At 9 weeks post-neoadjuvant CRT, participants were restaged using chest, abdomen, and pelvic CT and pelvic MRI. The colorectal Multi-Disciplinary Team was blind to PAL results and participant allocation.

Measurements

Daily PAL was measured in all participants using a multi-sensor accelerometer (SenseWear Pro® armband; BodyMedia, Inc., Pittsburgh, PADL, USA). The SenseWear Amrband Pro is a reliable estimation of resting EE and provides useful information on daily EE when compared to indirect calorimetry (cancer patients) [12] and reasonable agreement on daily EE when compared with doubly labelled water (free living-adults) [13]. The PA accelerometer was worn

on the upper right arm continuously for 3 consecutive weekdays (except when bathing). Participants in the exercise-training group removed the PA monitor during in-hospital exercise training sessions.

The armband estimates energy expenditure (EE) using measurements from a biaxial accelerometer and sensors that quantify galvanic skin response, heat flux and skin temperature The device records and reports daily movement: total and active EE; PA duration; number of steps; lying down time; average MET; sleep duration and efficiency (number of minutes of sleep divided by number of minutes in bed). The Sensewear Pro can distinguish between lying down and sleep time by using algorithms that detect the characteristics combination of orientation, motion, temperature and skin conductivity with each state.

Statistical methods

This was a nested study of a clinical trial, which was powered to detect changes in objectively measured physical fitness [10]. Therefore no a priori formal power calculation was undertaken for such a PA pilot study.

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%). The Shapiro-Wilk test for normality of distributions was applied. Descriptive statistics and univariate statistical comparisons of patient characteristics between the groups were undertaken: for continuous variables, a two- sample t-test when relevant distributional assumptions were met and the Mann–Whitney U-test otherwise; for categorical variables, $\chi 2$ tests or, when cell counts were insufficient, Fisher's exact test.

Generalized linear mixed models, with a repeated effect for the comparison between the consecutive visits, were used to obtain restricted maximum likelihood (REML) solutions with an unstructured type of the covariance matrix for all or selected measurements in the two

groups. Least square means with 95% CIs were obtained. P<0.05 was taken as statistically significant. All analyses were performed with the statistical software IBM SPSS Statistics Ver.22 (IBM Corporation, Armonk, NY, USA).

Results

A total of 39 participants were recruited of whom 23 (exercise group) and 10 (usual care control group) completed the study (6 participants dropped out of the usual care control group: 4 before baseline measurements and 2 during the study). There were significant baseline differences between groups in age, ASA and WHO performance status: the usual care control group were older with poorer subjective performance (Table 1). Further details of participant characteristics are reported elsewhere [10].

There was a significant reduction in daily step-count between pre neoadjuvant CRT (baseline) and post neoadjuvant CRT (week 0) in all participants (4966 (4435) vs. 3044 (3265); P<0.0001), active EE (kcal) (264 (471) vs. 154 (164); P<0.005), and MET (1.3 (0.6) vs. 1.2 (0.3) P<0.05; table 2)(Supplementary Table 1 shows overall PAL as mean (SD) and median and inter-quartile range (IQR). Following the 6-week exercise intervention, the exercise group compared to the usual care control group showed significant improvements in sleep efficiency (%) (78 (13) vs. 80 (15) compared to(69 (24) vs. 76 (20); P=0.022), sleep duration (min) (190 (269) vs. 369 (81) compared to (265 (315) vs. 299 (39); P=0.028) and lying down time (min) (360 (352) vs. 47 (476) compared to (541 (360) vs. 341 (372); P=0.029, table 3) (Supplementary Table 2 shows overall PAL data as mean (SD) and median and inter-quartile range (IQR). Note: (1) the exercise training group took the PA monitors off for the duration of each in-hospital exercise session (120 min/week x 6 weeks): (2) sleep efficiency data is presented in only seven participants in the exercise intervention and usual care control group: this is due to an upgrade in software during data collection.

241 **Table 1** Characteristics of patients scheduled for neoadjuvant cancer treatment and surgery

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	Exercise (n=23)	Control (n=10)	P value
Age (yr)*	64 (45-82)	72 (62-84)	0.015
Gender M:F (%)	15 (65): 8 (35)	8 (80): 2(20)	0.710
Past medical history[+]	10 (44)	5 (50)	0.617
Heart failure	3 (13)	1 (10)	
Diabetes	2 (9)	1 (10)	
Ischaemic heart disease	5 (22)	3 (30)	
Cerebrovascular disease	0	0	
ASA[±]			0.003
I	11 (48)	0	
II	10 (44)	9 (90)	
III	2 (9)	1 (10)	
WHO performance status[±]			0.035
0	18 (78)	0	
1	5 (22)	9 (90)	
2	0	1 (10)	

243 Values presented as mean (range). * P<0.05 was taken as statistically significant.

244 [+]Frequencies with percentages in parentheses, smoking status assessed as currently smoking: yes (1) vs no (0);
245 [±]number of patients (%) WHO performance status and ASA physical status. Participants who dropped out of the
246 study are not included in participant characteristics.

247 **Table 2** Pre- and Post- Neoadjuvant CRT physical activity variables
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Physical Activity Variables	Pre neoadjuvant CRT	Post neoadjuvant CRT	Change, % Change	P value
Step count (steps/day) *				
Exercise (n=23)	5705.3 (3746)	3723 (2867)	-2755 (4152), -44 (20)	
Usual care control (n=10)	3701.5 (3569)	2274 (3690)	-4 (2600), -0.1 (78)	
Overall (n=33)	4966 (4435)	3044.2 (3265)		<0.0001
MET*				
Exercise (n=23)	1.4 (0.5)	1.3 (0.4)	-0.03 (0.3), -2.3 (15)	
Usual care control (n=10)	1.3 (0.9)	1.1 (0.2)	-0.1 (0.3), -8 (14)	
Overall (n=33)	1.3 (0.6)	1.2 (0.3)		0.010
Active EE (kcal/day) *				
Exercise (n=23)	229 (482.3)	152 (153.7)	-115 (499), -30 (93)	
Usual care control (n=10)	354 (443.5)	244.3 (198.3)	-223 (861), -47 (70)	
Overall (n=33)	264.3 (471.3)	154 (163.9)		0.003
PA duration (min/day)				
Exercise (n=23)	61 (97.3)	38 (68)	31 (105), 8 (140)	

Physical Activity Variables	Pre neoadjuvant CRT	Post neoadjuvant CRT	Change, % Change	P value
Usual care control (n=10)	69 (83)	50 (4)	-34 (151), -41 (52)	
Overall (n=33)	64 (80.3)	39 (46)		0.45
Lying down (min/day)				
Exercise (n=23)	250 (367.3)	360 (351.7)	6 (211), 2 (40)	
Usual care control (n=10)	351.4 (432.4)	541.3 (360.4)	119 (263), 28 (71)	
Overall (n=33)	363 (423.9)	483.5 (416.5)		0.443
Sleep efficiency (%)				
Exercise (n=7)	78 (9.1)	78 (13)	0.2 (15), 0.3 (21)	
Usual care control (n=7)	69 (20)	69 (24)	-4 (23), -5 (30)	
Overall (n=14)	75 (11)	73 (22)		0.917
Sleep duration (min/day)				
Exercise (n=23)	220 (330)	190 (269)	0 (141), 0 (35)	
Usual care control (n=10)	264.5 (284)	265 (315)	143 (235), 56 (85)	
Overall (n=33)	260 (285)	44 (318)		0.847

Physical Activity Variables	Pre neoadjuvant CRT	Post neoadjuvant CRT	Change, % Change	P value
Total EE (kcal/day)				
Exercise (n=23)	1668 (932)	1701 (921)	-234 (1013), -0.1 (63)	
Usual care control (n=10)	1867 (833)	1741 (416)	-241 (1019), 7 (147)	
Overall (n=33)	1668 (846)	1707 (722)		0.33

Values presented as median (IQR) for: pre neoadjuvant CRT; post neoadjuvant CRT; change; and % change.
* P<0.05 was taken as statistically significant based on paired Wilcoxon test
All data is averaged over the 72 h period of PA monitoring. Abbreviations: EE – energy expenditure, PA – physical activity. Note: due to an upgrade in software during data collection, PAL and sleep efficiency is reported in 7/23 (exercise) and 7/10 (usual care control).
Note: Absolute change (with no brackets) and relative percentage change(in brackets)is reported between pre neoadjuvant CRT (baseline) to post neoadjuvant CRT (week 0) within the groups.

Table 3 Changes in physical activity variables (Week 0 - Week 6)

	Exercise				Usual care control				
	Week 0	**Week 3**	**Week 6**	**Change, % Change**	**Week 0**	**Week 3**	**Week 6**	**Change, % Change**	**P-value**
Step-count (steps/day)	3723 (2867)	6333 (5291)	5401 (3869)	-1544 (5800), -22 (52)	2274 (3690)	6422 (7158)	4792 (4370)	1580 (1732), 57 (70)	0.728
MET	1.3 (0.4)	1.5 (0.4)	1.5 (0.5)	-0.1 (0.6), -7 (38)	1.1 (0.2)	1.2 (0.3)	1.5 (0.5)	0.2 (2), 17 (174)	0.440
Active EE (kcal/day)	152 (154)	355 (486)	434 (658)	-181 (1228), -46 (92)	244 (198)	322 (517)	392 (701)	320 (1368), 110 (284)	0.743
PA duration (min/day)	38 (68)	76 (70)	84 (110)	-35 (185), 41 (105)	39 (46)	66 (89)	89 (132)	85 (243), 100 (276)	0.992
Lying down time (min/day)*	360 (352)	95 (438)	47 (476)	18 (332), 4 (82)	541 (360)	321 (352)	341 (372)	10 (292), 2 (82)	0.029

	Exercise				Usual care control				
	Week 0	**Week 3**	**Week 6**	**Change, % Change**	**Week 0**	**Week 3**	**Week 6**	**Change, % Change**	**P-value**
Sleep efficiency (%)*	78 (13)	78 (14)	80 (15)	-6 (28), -6 (39)	69 (24)	66 (14)	76 (20)	6 (11), 7 (17)	0.022
Sleep duration (min/day)*	190 (265)	405 (70)	369 (81)	0.0 (141), 1.0 -1.2 (52)	265 (315)	197 (244)	299 (39)	143 (235), 3 (112)	0.028
Total EE (kcal/day)	1707 (921)	1949 (769)	1869 (924)	-2 (1177), -0.1 (63)	1741 (416)	1962 (730)	1673 (1169)	147 (2705), 7 (147)	0.701

Values presented as median (IQR) for: pre neoadjuvant CRT; post neoadjuvant CRT; change; and % change.
*P<0.05 is taken as statistically significant. All data is averaged over the 72 h period of PA monitoring. Data for each group at each time point is presented.

Note: due to an upgrade in software at the time of data collection, PAL and sleep efficiency is reported in 7/23 (exercise) and 7/10 (usual care control).

Note: Absolute change (no brackets) and relative percentage change (with brackets) at week 6 from baseline ((pre-CRT), presented in table 2)) within the groups.

Discussion

This pilot study shows that neoadjuvant CRT significantly reduced daily step-count, active EE and MET in people with newly-diagnosed locally advanced rectal cancer. Furthermore, neoadjuvant CRT had a generally negative effect on the other exploratory PA variables, although findings were not statistically significant. People who participated in the 6-week in-hospital exercise training programme, in the time interval following neoadjuvant CRT and prior to surgery, showed significant improvements in sleep efficiency, sleep duration and lying down time compared to the usual care control group. Furthermore, the exercise group showed an improvement in daily step-count and active EE, although these findings did not reach statistical significance.

It has been previously been reported that neoadjuvant chemo- and chemoradio-therapy significantly reduce physical fitness and this change is associated with post-operative complications and reduced 1-year survival in locally advanced rectal and upper gastrointestinal cancer [2-3]. However, little is known about its effect on PAL and to our knowledge, we are the first to report daily PAL in people with locally advanced rectal cancer scheduled for neoadjuvant cancer treatment and surgery. PAL is commonly quantified by using metabolic equivalent (MET) which is scored as follows: ≥1.70 (active person); 1.40 – 1.69 (predominantly sedentary); < 1.40 (very inactive); and 1.2 (chair- or bed-bound) [14]. We reported a MET score at cancer diagnosis 1.3 (0.6) which significantly reduced to 1.2 (0.3) following neoadjuvant CRT. This MET score suggests that people in our study were sedentary following neoadjuvant CRT. Although findings were not statistically significant, we reported lying down time at cancer diagnosis 363 (424) minutes compared to 484 (417). We also reported, at cancer diagnosis prior to commencing cancer treatment, people in our study had a lower than recommended daily step-count (7,000 - 10,000) of 4966 steps (4435) which further reduced to 3044 steps (3265) following neoadjuvant CRT. Daily step count reported following

CRT in our study is comparable to daily step count reported in people living with Chronic Obstructive Pulmonary Disease (COPD) [15]. Although little is known about low levels of PA in people with cancer, low levels of PA in people with COPD is associated with development of systemic consequences such as skeletal muscle weakness, osteoporosis, cardiovascular disease PAL [16] and with hospital admission and mortality [17].

Participation in the exercise programme had a positive influence on PAL outside the programme similar to findings reported in other studies in people with breast cancer who participated in an exercise programme during adjuvant cancer treatment [18-19]. Although findings were not significant, we reported animprovement in active EE and MET following participation in the exercise programme initiated following neoadjuvant CRT and before surgery. We also showed that daily step-count at week 3 following neoadjuvant CRT almost doubled in both groups compared to week 0 but further reduced at week 6, more so in the usual care control group (it must be noted, there were no statistical changes in daily step-count following participation in the exercise programme therefore caution is required while interpreting our findings). Additionally, following participation in the exercise programme, there was a significant improvement in sleep efficiency (as well as sleep duration and lying down time) which may be clinically important: sleep disturbance in people with cancer is the second most common reported symptom [20]. Sixty-one percent of people with breast cancer undergoing chemotherapy and radiotherapy report having significant sleep problems (measured using Pittsburgh Sleep Quality Index) which is related to poor Health Related Quality of Life (HRQoL) [21]. To our knowledge, only one other study in people with breast cancer scheduled for multimodal treatment (surgery and adjuvant cancer treatment) has assessed sleep disturbance in the context of exercise training during cancer treatment (measured using General Sleep Disturbance response scale) [22]. Although findings from this

study did not reach statistical significance, there was a decline in sleep disturbance following a 12-week exercise programme.

To date, measures assessing PAL in people with cancer mainly include subjective self-reported measures such as: Short Form Health Survey (SF-36) [18, 23-24]; Physical Activity Questionnaire (PAQ) [23]; Scottish Physical Activity Questionnaire (SPAQ) [18]; and leisure time physical activity [19], all of which provide a patient's personal perception of their daily activities. Such questionnaires have been found to be of limited validity and reliability [25]. Patients' estimations of time spent on activities has been shown to be inconsistent when compared to values recorded using PA monitors [24]. PA monitors have been validated as a measure of PAL in several patient cohorts such as in people with physical disabilities, COPD [26-28] and spinal cord injury [29]. PA monitors provide direct measures of specific behaviours such as steps per day [30] as well as the time spent being active (intensity of activity), standing, sitting and lying [28]. One recent study reported that cancer patients participating in a lifestyle intervention during chemotherapy reported 366% higher Moderate-to-Vigorous Intensity PA (MPVA) using the International PA questionnaire compared to measures collected using SenseWear accelerometers [31]. Our study highlights that objective measures of PAL throughout the cancer care journey are worthy of attention: they are relatively simple to undertake and to date have not been used in the perioperative setting.

Strengths of this study include its prospective design, the homogenous study population (only operable locally advanced rectal cancer patients), the clearly defined exercise intervention and the standardised neoadjuvant CRT regime. PA was averaged over a 72 hour period, measured in an objective manner using validated Sensewear activity monitors. Furthermore participants in the exercise group did not wear the PA monitors during exercise sessions. Potential weaknesses of this study include its design as a relatively small pilot study, which was powered

to detect changes in objectively measured physical fitness [10], and the limitation of recruitment to one single centre, which may limit generalisability of results. This was a non-randomised design study (i.e. participants in the usual care control group were people who were living >15 miles from the hospital) and there was significant baseline differences between groups in age, ASA and WHO performance status: the usual care control group were older with poorer subjective performance. Furthermore, differences exist in group sample size, 23/23 (exercise) and 10/16 (usual care control) completed the study. Sleep efficiency data were only available for 7 in each group: this was due to an upgrade in software during data collection.

Conclusion

Our study shows that neoadjuvant CRT significantly reduces MET score, active EE and daily step-count in people with locally advanced rectal. People who participated in a 6-week in-hospital exercise training programme following neoadjuvant CRT showed a significant improvement in sleep efficiency, sleep duration and lying down time and an apparent improvement in daily step-count and overall PAL compared to the usual care control group.

LIST OF ABBREVIATIONS

PAL, Physical activity levels; CRT, Chemoradiotherapy; EE, Energy expenditure; MET, Metabolic equivalent threshold; CPET, Cardiopulmonary exercise test; PA, Physical activity; TNM, Tumour, Nodes, Metastasis; MRI, Magnetic Resonance Imaging; CT, computer-aided tomography; SD, standard deviation; IQR, Inter-Quartile Range; REML, restricted maximum likelihood; COPD, Chronic Obstructive Pulmonary Disease; HRQoL, Health Related Quality of Life;. SF-36, Short Form Health Survey; PAQ, Physical Activity Questionnaire; SPAQ, Scottish Physical Activity Questionnaire.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the North West Liverpool East Research and Ethics Committee (11/H1002/12) and registered with clinicaltrials.gov (NCT01325909). Written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and material

The datasets from the current studycan be made available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MAW, GJK, MPWG and SJ conceived the study. LL, MAW, GJK, MPWG and SJ contributed to study design. BDD undertook the statistical analysis. LL drafted the manuscript which underwent revision by all other authors. All authors read and approved the final manuscript.

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FIGURE LEGENDS

Figure 1. The patient pathway and the time points of assessments.