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Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors—results from a pilot study

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Abstract

The aims of this pilot study were to compare aerobic capacity in non-fatigued and fatigued Hodgkin's disease survivors (HDS) and to assess the feasibility of an exercise-programme and its effects upon fatigue, physical functioning and aerobic capacity in chronic fatigued HDS. 53 HDS (85%) of originally 62 survivors treated at the Trondheim University Hospital in the period 1987–1997 completed a questionnaire including the Fatigue Questionnaire (FQ). 18 subjects were identified with chronic fatigue. 15 non-fatigued HDS matched for gender and age were drawn as controls. Both groups were invited to medical examination and exercise tests. All 15 fifteen non-fatigued HDS showed up to the medical examination. 12 of the 18 patients with chronic fatigue completed the tests and nine agreed to enter a home-based exercise intervention. Outcome measures were aerobic capacity, fatigue and physical functioning. No significant difference in aerobic capacity was found between the chronic fatigued HDS and the controls. Fatigue, physical functioning and maximal aerobic capacity were significantly improved after the intervention. Aerobic exercise had a positive effect upon chronic fatigue in HDS. However, the study is a pilot study and needs confirmation in a larger group of subjects. The intervention was well accepted, and the majority of the patients adhered to the programme.

Keywords: Exercise; Fatigue; Intervention study; Hodgkin's disease

1. Introduction

The prevalence of chronic fatigue among Hodgkin's disease survivors (HDS) is 25–30% compared with 11% in the general population [1]. Fatigue seems to be more prevalent in HDS than in other cancer survivors [2]. Chronic fatigue in this particular group of cancer survivors is relatively poorly understood, but an association between fatigue and pulmonary dysfunction has recently been demonstrated [3].

Fatigue is a normal and passing experience after physical and mental exertions, and contributes to regulate the balance between rest and activity, resulting in restoration when needed. For example, some days of rest are a normal and effective strategy in the restitution after an acute infectious disease. Patients undergoing treatment for cancer are often advised to limit their activity and get enough rest. These strategies may be effective in acute situations of fatigue. However, for patients suffering from chronic fatigue, rest will result in physical deconditioning and probably increased fatigue. Most individuals with chronic disease or disability become less physically active, and this may lead to a cycle of deconditioning of multiple physiological systems [4]. Many chronic diseases such as cognitive heart failure, multiple sclerosis, systemic lupus erythematosus and patients with psychiatric disorders are accompanied by fatigue [5–8]. Like in chronic pain, the experience of fatigue in chronic disease may provoke psychological and biological reactions that maintain or exacerbate fatigue in a vicious circle. Furthermore, prolonged rest or inactivity can lead to skeletal muscle atrophy and

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further reduction in exercise tolerance. Today, however, there is increasing consensus among professionals that persistent rest may worsen fatigue in sufferers of the chronic fatigue syndrome (CFS) [9].

There is no consensus on how to prevent or alleviate fatigue. In a randomised clinical trial (RCT), graded aerobic exercise significantly improved fatigue, functional capacity and fitness in CFS patients without psychiatric or sleep disorders compared with flexibility exercises and relaxation therapy [10].

Exercise is one of the few interventions suggested to prevent or decrease fatigue among cancer patients, but the research supporting this is limited [11–13]. Dimeo and colleagues concluded that an aerobic exercise programme improved maximal physical performance and reduced fatigue in fatigued cancer patients. However, these studies mainly included cancer patients during and immediately after chemotherapy or radiotherapy [13,14].

To our knowledge, no published study has so far tested exercise capacity among chronic fatigued HDS or the effects of physical exercise in chronic fatigued cancer survivors. On this basis, the present quasi-experimental pilot study was conducted to examine the level of aerobic capacity among chronic fatigued HDS compared with HDS without chronic fatigue. Further aims were to assess the effects of an aerobic training programme upon fatigue, physical functioning and aerobic capacity in chronic fatigued HDS and to evaluate the feasibility of the programme as a preparative step for a larger randomised study.

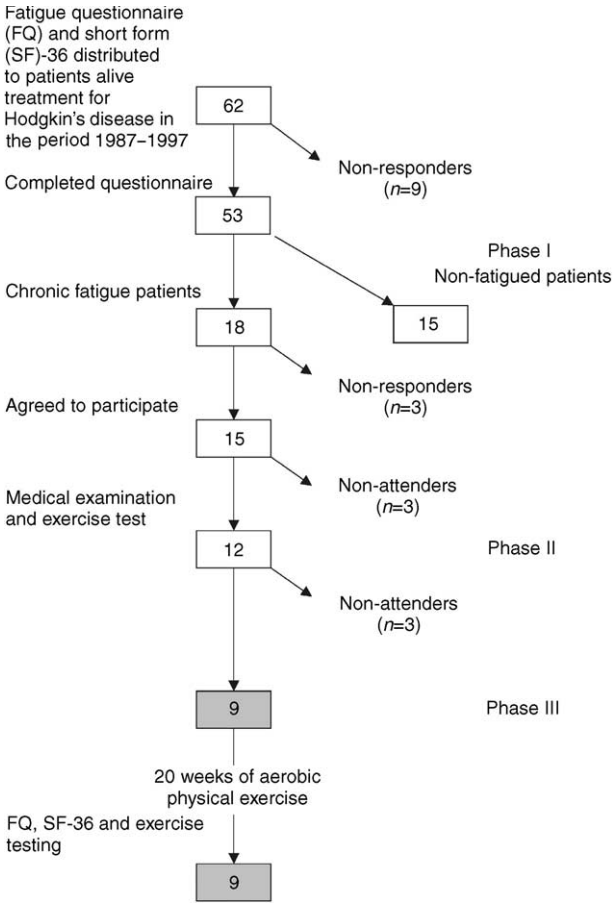

Fig. 1. Flow chart of the survey and intervention patients.

2. Material and methods

2.1. Sampling

Fig. 1 shows the flowchart of the study and the patient selection. The study included three phases; phase 1 is a survey; phase 2 is an exercise testing and medical examination and phase 3 is an intervention study. 62 patients (aged 19–74 years) were treated for Hodgkin's disease at the University Hospital in Trondheim in the period 1987–1997 and were alive without active disease in 1999. They were approached by mail, and 53 patients completed the questionnaires after one written reminder (85%). 18 of the 53 patients reported chronic fatigue (34%) (*phase I*). These were invited to participate in medical examinations and physical exercise testing. 15 of the 18 chronic fatigued patients gave their consent to participate at this stage. The reasons for not participating were living too far away from the hospital ($n=2$) and unknown reason ($n=1$). 12 of the 15 patients completed the physical exercise testing and the medical examinations. One person did not show up in spite of two reminders. Two subjects underwent the medical examination, but were not able to perform the physical exercise test because of a splint in the leg ($n=1$), and relapse of the malignant disease ($n=1$) (*phase II*). After the medical examinations and the exercise test the cohort was invited to participate in an intervention consisting of aerobic exercise three times a week for 20 weeks. 9 of the 12 patients (4 women and 5 men) gave written informed consent and entered the intervention (*phase III*). Two men wanted to perform individual exercise by themselves, but did not want to attend the programme. One woman was too ill to take part in the exercise programme.

From the 35 non-fatigued HDS who had completed the questionnaire, 15 patients of same gender and age ± 2 years were drawn as controls (see Fig. 1). After giving written informed consent, the controls underwent exercise testing and medical examinations identical to the chronic fatigued survivors, but were not offered the training programme.

Patient characteristics in the non-fatigued and the fatigued HDS are presented in Table 1. The distribution of the demographic characteristics and time since treatment was well balanced between the two groups.

2.2. Subjective health assessments

Fatigue was assessed by the Norwegian version of the Fatigue Questionnaire (FQ) [15]. The FQ is a self-report

Table 1
Samples characteristics

	HDS with fatigue $N=12$	HDS without fatigue $N=15$	P value
Age (years)			
Mean (S.D.) (range)	41 (11.3) 24–58	40 (11.0) 25–60	NS
Gender (N (%))			
Male	7 (58)	9 (60)	NS
Female	5 (42)	6 (40)	
Educational level N (%)			
$\leqslant$10 years	6 (50)	9 (60)	
$\geqslant$11 years, university $<$4 years	3 (25)	2 (13)	NS
University $\geqslant$4 years	3 (25)	4 (27)	
Stage/substage N (%)			
IA/IIA	9 (75)	10 (67)	
IB/IIB	1 (8)		NS
IIIA/IVA		3 (20)	
IIIB/IVB	2 (17)	2 (13)	
Primary treatment N (%)			
Radiotherapy	5 (42)	5 (33)	
Chemotherapy	4 (33)	3 (20)	NS
Radiotherapy + chemotherapy	3 (25)	7 (47)	
Relapse	2 (17)	3 (20)	NS
Smoker	5 (42)	2 (13)	NS
Work situation			
Paid work/trader	9	13	
Disabled/rehabilitation[a]	2	1	NS
House work	1.0	1	
Marital status			
Married/cohabitant	10	13	
Single/widowed	2	2	NS
Time since treatment (months)			
Mean (S.D.)	79 (35)	59 (32)	NS

S.D., standard deviation; HDS, Hodgkin's disease survivors; NS, non-significant.
[a] One person had a 50% disability pension and was also in paid work.

instrument for the assessment of fatigue including symptoms experienced during the last month, compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and the extent of fatigue. FQ measures physical fatigue (PF) (seven items) and mental fatigue (MF) (four items). All 11 items are designated total fatigue (TF). Each item has four response choices. Likert-scoring (0, 1, 2, 3) is used for construction of PF, MF and TF. Higher scores imply more fatigue. A dichotomised score (0, 0, 1, 1) is used for the definition of chronic fatigue, which is defined by sum of dichotomised scores $\geqslant$4 and duration 6 months or longer. The FQ has originally been validated in primary care and has shown good face and discriminant validity. No specific validation study has been performed in cancer patients. However, the FQ has been used in studies among Hodgkins disease survivors and in patients with prostate cancer receiving hormonal therapy [1,16]. The psychometric properties demonstrated in these studies correspond with reports from the validation study and from the studies in non-cancer populations. The FQ was filled in before (*phase 1*) and immediately after the intervention period (end of *phase 3*) and was defined as the primary outcome of the intervention.

The SF-36 was completed before (*phase 1*) and immediately after the intervention period (end of *phase 3*) [17]. The sub-scale 'physical functioning' (10 items) was used as a secondary outcome-measure in the intervention. The responses were summed and transformed to a 0–100 scale (0 = worst health state, 100 = best health state) according to the SF-36 algorithm [18].

2.3. Physiological assessments

The patients height, weight, resting heart rate, resting blood pressure, maximal oxygen consumption (VO_{2max}), total walking distance/time to exhaustion and heart rate at sub-maximal and maximal speed were measured immediately before and after the intervention programme. The patients were instructed not to perform heavy exercise training nor to smoke or eat 2 h before the test. Lung function was measured before the clinical examination in both groups.

2.4. Physical exercise capacity

VO_{2max} was measured by use of a cardiopulmonary exercise testing instrument (Vmax29, Sensomedics, Netherlands). The patients were walking and running on a treadmill. The heart rate was measured continuously during the test using a Polar Sport tester PE 3000.

For assessment of maximal physical performance the Oslo protocol was used [19]. The test protocol (speed and elevation increment) was carried out until exhaustion.

2.5. Lung function measurements

The lung function test included dynamic spirometry. Spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and FEV_1 expressed as percent of FVC (FEV_1%). The tests were performed using Vmax29 testing instrument (Sensomedics, The Netherlands).

2.6. Intervention procedure

An exercise instructor visited the patients in their local community at the start of the exercise period. The patients were given instructions and advice in their home-based exercise programme. The Polar Sport Tester recorded and stored the pulse rate every fifteenth second during the exercise session. Follow-up phone calls were done regularly to motivate, guide and regulate the intensity of the exercise programme.

Table 2
Physiological comparisons of the fatigued and non-fatigued patients

	HDS with chronic fatigue ($n=12$) (mean) (95% CI)	HDS without chronic fatigue ($n=15$) (mean) (95% CI)	P value
Weight (kg)	78.2 (72.8–83.6)	74.7 (67.8–81.5)	NS
Height (cm)	176 (170–182)	173.7 (170–177.5)	NS
BMI (kg/m^2)	25.2 (24.8–26.4)	24.7 (22.8–26.6)	NS
VO_2 peak (ml kg^{-1} min^{-1})	32.7 (27.1–38.2)	34.0 (29.5–38.6)	NS
Resting heart rate (beats/min)	81 (72–91)	79 (68–89)	NS
Lung function variables[a]			
FVC	104 (90–118)	94 (84–103)	0.04
FEV_1	97 (85–110)	93 (83–104)	NS
FEV_1%	78 (76–81)	82 (78–87)	NS
Maximal heart rate (beats/min)	184 (174–194)	185 (170–194)	NS

BMI, Body Mass index; 95% CI, 95% Confidence Interval.
[a] Lung function values are presented as percentage of predicted normal values.

2.7. Aerobic endurance exercise programme

The aerobic endurance exercise programme consisted of 20 weeks with an exercise session of 40–60 min continuous work using large muscle groups at an intensity of 65–80% of the subjects target heart rate (measured at the first test) three times a week. An exercise diary filled in by the patients contained information on the duration, type of activity as well as the patients' experience of the exercise session classified as 'easy', 'somewhat strenuous' or 'strenuous'. The activities could be chosen and included brisk walking, jogging, bicycling, aerobics, cross-country skiing or swimming. The attainment target for compliance was 75% of the aerobic exercise programme. This is considered to be minimum attendance accepted in other similar studies [20].

2.8. Data scores and statistical analysis

All statistical analysis was performed using the Statistical Package for the Social Services (SPSS) software package (8.0 for Windows) with two tailed tests for estimates of P values. The 0.05 criteria were used to define statistically significant effects. The statistical analysis included Chi-tests statistics (categorial variables) and Student t-tests were used to assess pair-wise group differences. Analysis was carried out on an intention-to-treat basis.

3. Results

3.1. Fatigued versus non-fatigued HDS

Results from physiological comparisons of the fatigued and the non-fatigued HDS are presented in Table 2. No statistically significant differences were seen between the two groups in physiological measures: body mass index (BMI), VO_2 peak, resting heart rate, maximal heart rate or resting blood pressure. Spirometric variables did not differ significantly between the two groups, except for FVC ($P=0.04$). The FVC mean value of the chronic fatigued HDS was 4% above the mean normal value, while the controls' mean value was 6% below the mean normal value. However, both groups scored within the FVC normal range as recommended by the European Respiratory Society [21].

All the 9 patients who attended the intervention completed the pre- and posttests. There were no statistically significant differences between patients who completed the intervention programme ($n=9$) and the non-respondents/non-attenders ($n=9$) by gender, age, relapse, primary treatment, marital status, work situation, time since treatment, fatigue scores, physical function or work situation. However, the education level among the two groups indicated a borderline significant difference in favour of a higher proportion of university education in the intervention group ($P=0.06$). Time since antitumour therapy and inclusion in the study was 82 months standard deviation (S.D.) 41.6) in the intervention group.

6 of the 9 patients adhered to the prescribed programme according to the results from the Polar Sport tester, the written exercise diary, regularity and compliance of 75% of the instructed exercise hours. The 3 others exercised more sporadically.

3.2. Effects of intervention upon subjective outcomes

After the training period, the TF score was reduced by 43.7% in the intervention group ($n=9$) from 21.5 before the intervention to 12.1 after the intervention ($P=0.001$). PF was reduced by 43.6% from 14.0 to 7.9 ($P<0.001$). MF was reduced by 44.0% from 7.5 to 4.2 ($P=0.01$). (Table 3). 7 of the 9 patients scored below the

Table 3
Subjective health effects of the intervention

	Before exercise ($N=9$) (95% CI)	After exercise ($N=9$) (95% CI)	P value
Total fatigue (mean)	21.5 (18.7–24.4)	12.1 (9.6–14.6)	$P=0.001$
Mental fatigue (mean)	7.5 (5.7–9.4)	4.2 (3.3–5.1)	$P=0.01$
Physical fatigue (mean)	14.0 (12.4–15.6)	7.9 (5.6–10.1)	$P<0.001$
Physical function (mean)	82.2 (72.6–91.8)	89.4 (80.7–98.1)	$P=0.04$

95% CI, 95% Confidence Interval.

threshold (dichotomised score $\geqslant 4$) for chronic fatigue after completing the intervention. All 6 patients who adhered to the exercise program were among these. The score on the physical functioning scale was improved from 82.2 before start of the exercise period to 89.4 postintervention ($P=0.04$).

3.3. Physiological effects of the intervention

VO_{2max} increased from 33.9 ml kg^{-1} min^{-1} (pre) to 36.0 ml kg^{-1} min^{-1} (post) ($P=0.04$) (Table 4). Time to exhaustion on the treadmill increased from 11 min and 30 s to 13 min and 20 s ($P=0.04$). The sub-maximal heart rate in all sub-maximal speeds and inclinations were reduced from before to after the exercise period at 20 weeks. Body mass index, resting heart rate, target heart rate under exercise testing did not show any significant differences from pre- to post-test.

4. Discussion

Exercise capacity (VO_{2max}) did not differ between the chronic fatigued HDS and HDS without chronic fatigue. Therefore, aerobic exercise capacity does not seem to play an important role in the pathophysiology of chronic fatigue in HDS. The reduction of fatigue after 20 weeks of aerobic exercise indicate that home-based physical exercise may be an alternative treatment for chronic fatigued HDS. Furthermore, the feasibility and adherence rate compare with well to similar exercise intervention studies [22]. VO_{2max} was significantly improved after the intervention.

Interpreting the clinical significance of differences is of greater relevance than the statistical significance level *per se*. According to Osoba's division of difference in health related quality of life scores (HRQOL scores) on a 0–100 scale, scores between 5 and 9 are little differences 10–20 moderate and >20 large differences. Improvement in previous studies of 10–15% was considered clinically significant [23]. The improvement in physical functioning from 82.2 to 89.4 is statistically significant at the 0.05 level in our study. However, according to Osoba the clinical significance is low. Nevertheless, the reduction in all three fatigue scores (FT, PF and MF) of approximately 44% should be considered clinically significant. Similar numerical reductions in fatigue in randomised trials among sufferers of the CFS have been found after cognitive behaviour therapy and graded physical exercise [10,24]. The level of fatigue after the intervention in the present study is at the same level as in the general Norwegian population [1].

An aerobic exercise programme can break the circle of inactivity, impaired performance and increased fatigability [11]. However, the specific mechanisms for the effects are still not fully understood. One could speculate whether subjects without chronic fatigue already use physical exercise as a means to reduce fatigue. Dimeo and colleagues observed an improvement in maximal physical performance and a clear reduction in fatigue after daily walking on a treadmill in five cancer survivors [25]. However, the cohort was heterogeneous with regard to cancer diagnoses and the patients were studied relatively close to termination of cancer-specific treatment (8 weeks–9 months). The improvement may therefore reflect the natural course of fatigue after termination of cancer treatment.

No study has to our knowledge investigated differences in physical exercise capacity among HDS with and without chronic fatigue. Studies on exercise capacity and related cardiopulmonary variables in CFS patients have produced contradictory results [26]. However, CFS-patients show significantly lower exercise capacity than healthy subjects [27,28]. The present results did not confirm such a pattern in HDS.

All 15 patients among non-fatigued HDS attended the tests. A possible reason for the 100% attendance rate in

Table 4
Physical effects of the intervention

	Before exercise ($N=9$) (mean) (95% CI)	After exercise ($N=9$) (mean) (95% CI)	P value
VO_{2peak} (ml kg^{-1} min^{-1})	33.9 (29.9—37.9)	36.0 (31.0–41.1)	$P=0.04$
Maximal walking time (min.s)	11.30 (9.30–12.40)	13.20 (11.10–15.40)	$P=0.04$
Weight (kg)	77.3 (70.0–84.7)	77.0 (69.0–85.0)	NS
Resting heart rate (beats/min)	80 (72–89)	76 (69–83)	NS
Maximal heart rate (beats/min)	192 (180–198)	189 (181–197)	NS

CI, 95% Confidence Interval; NS, non significant.

the control group is less additional medical problems, which is supported by the observation/fact that the fatigued patients gave various medical reasons for not attending the study.

Completion of training depends on factors such as motivation, education, knowledge of, and belief in the beneficial effects of physical activity on health, weight and mental health [29]. Our finding towards a higher educational level in the intervention group supports this. This raises the important question of whether exercise intervention/rehabilitation is for a selected group. Other interventions may be more suitable for other patients. Unfortunately, we do not have any information about earlier exercise habits in the subject group. The drop-out rate in the intervention group is quite similar to other exercise studies [30]. Studies on healthy populations have consistently shown that 50% of individuals who begin a structured exercise programme will drop out within the first 6 months [22]. 6 of the 9 patients who entered the intervention adhered to the prescribed programme. Thus the total drop-out rate was 33%. The three drop-outs completed the objective and subjective pre- and posttests, but were more sporadic exercisers according to the exercise diaries and stored pulse rate results.

The absence of a control group limits the possibility of drawing firm conclusions on the effects of aerobic exercise. The effects could be a Hawthorne-effect (non-specific placebo effect). However, previous reports have shown that aerobic exercise significantly improves physical performance, reduces levels of fatigue and increases quality of life in both CFS patients and patients in early rehabilitation after cancer treatment [10,14,31]. Furthermore, the documented adherence to the programme and the improved physical capacity also weaken the probability for a Hawthorne effect explaining our findings.

Instructed home exercise was chosen before group exercise because most of the patients lived too far away from the hospital. In addition, we wanted to simulate real life conditions in order to assess the feasibility of the intervention.

Rehabilitation programmes of cured cancer patients has been proposed to be a standard offer. However, extensive research may be needed. In studies evaluating such programmes, costs should be taken into considerations along with primary outcome of the effect of the intervention. The physical exercise programme in the present intervention is cheap and easy to carry out for selected and motivated patients. In addition to the favourable health effects, the home-based programme demonstrated feasibility comparable to more extensive and expensive programmes [32,33].

The generalisability of the findings is limited for several reasons. Firstly, this is a small pilot study. The number of patients was low ($n=9$), and the strength of the statistical analysis is therefore limited. Although the effect size is great and must be considered as clinically significant, studies with a comparable and randomised design are necessary in order to confirm these findings. Future studies are also needed to assess the feasibility of such an intervention and attempts should be made to simulate real life conditions.

Furthermore, this selected group should be followed over time to observe any possible long-term effects.

References

1. Loge JH, Abrahamsen AF, Ekeberg O, *et al*. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999, **17**, 253–261.
2. Bloom JR, Fobair P, Gritz E, *et al*. Psychosocial outcomes of cancer: a comparative analysis of Hodgkin's disease and testicular cancer. *J Clin Oncol* 1993, **11**, 979–988.
3. Knobel H, Havard LJ, Brit LM, *et al*. Late medical complications and fatigue in Hodgkin's disease survivors. *J Clin Oncol* 2001, **19**, 3226–3233.
4. Durstine JL, Painter P, Franklin BA, *et al*. Physical activity for the chronically ill and disabled. *Sports Med* 2000, **30**, 207–219.
5. Wysenbeek AJ, Leibovici L, Weinberger A, *et al*. Fatigue in systemic lupus erythematosus. Prevalence and relation to disease expression. *Br J Rheumatol* 1993, **32**, 633–635.
6. Krupp LB, LaRocca NG, Muir-Nash J, *et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989, **46**, 1121–1123.
7. Clark AL, Sparrow JL, Coats AJ. Muscle fatigue and dyspnoea in chronic heart failure: two sides of the same coin? *Eur Heart J* 1995, **16**, 49–52.
8. Drexler H, Coats AJ. Explaining fatigue in congestive heart failure. *Annu Rev Med* 1996, **47**, 241–256.
9. Sharpe M, Wessely S. Putting the rest cure to rest—again. *Br Med J* 1998, **316**, 796.
10. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *Br Med J* 1997, **314**, 1647–1652.
11. Dimeo F, Fetscher S, Lange W, *et al*. Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood* 1997, **90**, 3390–3394.
12. Winningham ML, Nail LM, Burke MB, *et al*. Fatigue and the cancer experience: the state of the knowledge. *Oncol Nurs Forum* 1994, **21**, 23–36.
13. Porock D, Kristjanson LJ, Tinnelly K, *et al*. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. *J Palliat Care* 2000, **16**, 30–36.
14. Dimeo FC, Tilmann MH, Bertz H, *et al*. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer* 1997, **79**, 1717–1722.
15. Chalder T, Berelowitz G, Pawlikowska T, *et al*. Development of a fatigue scale. *J Psychosom Res* 1993, **37**, 147–153.
16. Stone P, Hardy J, Huddart R, *et al*. Fatigue in patients with prostate cancer receiving hormone therapy. *Eur J Cancer* 2000, **36**, 1134–1141.
17. Ware Jr JE, Keller SD, Gandek B, *et al*. Evaluating translations of health status questionnaires. Methods from the IQOLA project. International Quality of Life Assessment. *Int J Technol Assess Health Care* 1995, **11**, 525–551.
18. How to Score the SF-36 Health Survey. Medical Outcomes Trust, Boston, 1994.

19. Fredriksen PM, Ingjer F, Nystad W, *et al*. Aerobic endurance testing of children and adolescents–a comparison of two treadmill-protocols. *Scand J Med Sci Sports* 1998, **8**, 203–207.
20. Norris R, Carroll D, Cochrane R. The effects of aerobic and anaerobic training on fitness, blood pressure, and psychological stress and well-being. *J Psychosom Res* 1990, **34**, 367–375.
21. Standardized lung function testing. *Eur Respir J*. 1993, **6**, 5–53.
22. Dishman DK. Determinants of participation in physical activity. In Bouchard C, Shepard RJ, Stephens T, *et al*., eds. *Exercise, Fitness and Health: A Consensus of Current Knowledge*. Champaign, IL, Human Kinetics, 1990, 9–10.
23. Osoba D, Rodrigues G, Myles J, *et al*. Interpreting the significance of changes in health-related quality-of- life scores. *J Clin Oncol* 1998, **16**, 139–144.
24. Deale A, Chalder T, Marks I, *et al*. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry* 1997, **154**, 408–414.
25. Dimeo F, Rumberger BG, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exerc* 1998, **30**, 475–478.
26. Inbar O, Dlin R, Rotstein A, *et al*. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. *Med Sci Sports Exerc* 2001, **33**, 1463–1470.
27. Kent-Braun JA, Sharma KR, Weiner MW, *et al*. Central basis of muscle fatigue in chronic fatigue syndrome. *Neurology* 1993, **43**, 125–131.
28. Riley MS, O'Brien CJ, McCluskey DR, *et al*. Aerobic work capacity in patients with chronic fatigue syndrome. *Br Med J* 1990, **301**, 953–956.
29. Robinson JIRM. Adherence to exercise programmes: recommandations. *Sports Med* 1994, **17**, 39–52.
30. Kellett KM, Kellett DA, Nordholm LA. Effects of an exercise program on sick leave due to back pain. *Phys Ther* 1991, **71**, 283–291.
31. Wearden AJ, Morriss RK, Mullis R, *et al*. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry* 1998, **172**, 485–490.
32. Aastrand PO, Grimby G. Physical activity in health and disease. *Acta Med Scand*, 1986, 2.
33. Paffenberger RS, Hyde RT, Wing AL *et al*. Some interrelations of physical activity, physiological fitness, health and longevity. In Bouchard C, Shepard RJ, Stephens T, *et al*. eds. *Physical Activity, Fitness and Health: International Proceedings and Consensus Statement*. Champaign, IL, Human Kinetics, 1990, 33–45.