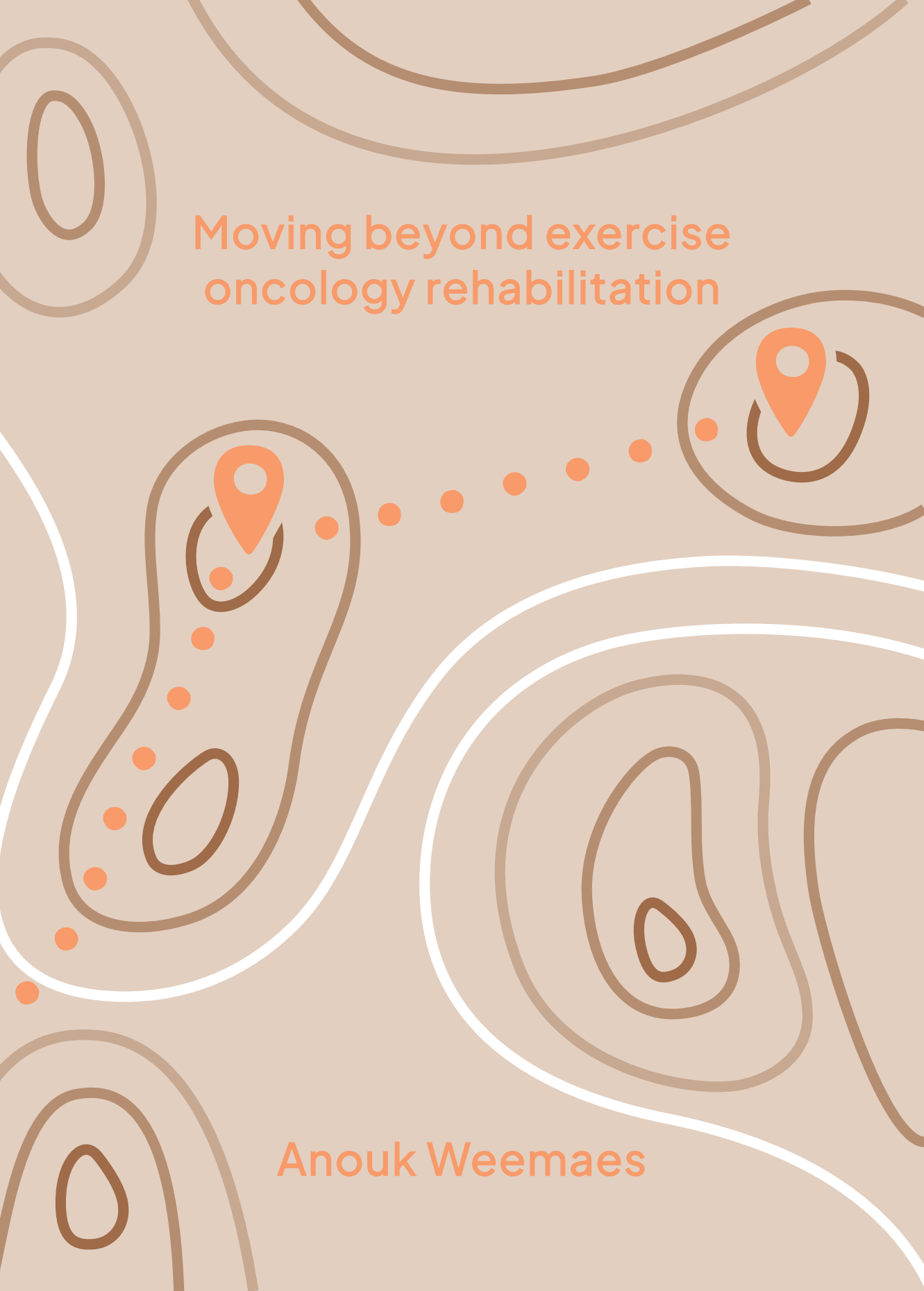


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Moving beyond exercise oncology rehabilitation

Anouk Weemaes

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Anouk T.R. Weemaes

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in het openbaar te verdedigen
op vrijdag 22 maart 2024 om 10.00 uur

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CHAPTER 1

General introduction



Cancer as a chronic disease

Receiving a diagnosis of cancer is an acute, life-changing event for patients and their relatives, and the patient journey of cancer is often described as a 'rollercoaster'. After the diagnosis, a treatment plan is made in agreement with the patient, which can involve surgery, systemic therapy (e.g. chemotherapy, hormone therapy, and immunotherapy), radiation, and stem cell therapy.^{1,2} These treatments and the disease itself can cause detrimental side effects like pain, declined physical fitness, fatigue, mental distress, and a diminished health-related quality of life (HRQoL).³⁻⁷ Side effects can persist for many years and can result in decreased physical activity (PA) levels, difficulties with returning to work and social functioning, and a high healthcare consumption.^{2,8,9}

Over the past decades, the incidence of cancer in the Netherlands increased rapidly. To illustrate, the absolute number of new cases increased from 103,638 in 2012 to 124,109 in 2022, and as a crude rate, from 619 new diagnoses per 100,000 inhabitants in 2012 to 706 per 100,000 inhabitants in 2022.¹⁰ The main reason for this is a demographic transition, with relatively more older people in the population and more people reaching an older age¹¹, as well as cancer being more common in older people. In addition, changes in lifestyle play a role, as is shown by a considerable rise in the incidence of cancers associated with poor lifestyle (e.g. breast and colorectal cancer).¹² It is estimated that approximately one-third of cancer cases could be prevented by reducing exposure to risk factors.¹ Being overweight (body mass index $>25\text{kg/m}^2$) and physical inactivity (<150 min moderate-intensity PA/week) are important modifiable risk factors for the development of cancer and are currently present in 39% and 28% of the global adult population, respectively.¹³⁻¹⁵ Finally, improved diagnostic modalities and national screening programs have led to better detection and consequently earlier and temporarily more diagnoses of cancer.^{1,2}

Not only diagnostic tools but also treatment options progressed quickly, leading to better survival or longstanding treatment with palliative care. The combination of increased incidence and improved survival rates has led to a substantial raise in the number of people living with or beyond cancer (hereafter: cancer survivors). It is expected that in 2032, 1 out of 13 people in the Netherlands will be living with a (previous) diagnosis of cancer. Hence,

for a large part, cancer is shifting from an acute and life-threatening disease, to a more chronic condition.^{1,2,16}

Modifiable risk factors for developing cancer are also related to other chronic conditions such as diabetes and cardiovascular disease and therefore the combined occurrence of cancer and other chronic diseases is not uncommon, especially within an ageing population. In a Dutch cohort study of patients with stage I-III colorectal cancer, 77% of all patients suffered from one or more comorbidities six weeks post-treatment.¹⁷ Recovery and management of side effects resulting from cancer and its treatment can be complicated by multimorbidity. Complex care needs that come along with this require integrated teams with expertise for optimal survivorship care.^{18,19} Research questions addressed in the current thesis were formulated based on literature combined with clinical observations from a supervised exercise program as part of multidisciplinary oncology rehabilitation, which is part of usual care at the Maastricht University Medical Centre (MUMC+) (Box 1.1).

As physical therapists involved in multidisciplinary oncology rehabilitation, my colleagues and I have personally witnessed the impact of cancer and its treatment on cancer survivors. Not only have they lost their physical fitness and muscle mass, but also the confidence in the functioning of their own bodies and their abilities to participate in their social activities and work. Physical therapists are the experts of functional movement and can help patients to rebuild physical fitness, but a multidisciplinary approach is required to solve the complex, interrelated health issues that cancer survivors can be confronted with. While guiding these patients through their recovery in a multidisciplinary team, my colleagues and I have been measuring physical fitness and collecting patient-reported outcomes over the years. However, in the hustle and bustle of a hospital environment, measurements were not always consistent and we had never looked further into outcomes. Research has shown beneficial effects of rehabilitation programs, but we questioned whether these results were translatable to the cancer survivors in our program.²⁰ Moreover, we questioned if cancer survivors were able to stay active after completion of the exercise program and if the improvements in physical fitness and patient-reported outcomes were sustained or further increased. We felt this was an important question to answer, because what would be the point of offering patients the best possible rehabilitation program, if they would lose the progress they gained a few months later, anyway? I was lucky to get the opportunity to learn more about oncology rehabilitation during my PhD research project. Working as an embedded scientist, combining research with my work as a clinical physical therapist, enabled me to answer these questions arising during daily care. These observations in the clinical field and critical discussions with colleagues have inspired me to conduct the studies presented in this thesis.

Box 1.1 Personal observations from the clinical field.

Survivorship care

The patient journey of cancer does not end after completing medical treatment. Where cancer treatment focuses mainly on overall and disease-free survival, the importance of HRQoL has been increasingly recognised. Adequate survivorship care along the continuum of cancer care is needed to reduce the disabling effects of cancer and possible comorbid conditions, and rehabilitation is an essential part of this.^{20,21} Research in the

field of exercise rehabilitation in cancer survivors expanded over the last decades, and growing evidence emerged for the positive effects of exercise on the adverse effects of cancer and its treatment.²²⁻²⁴ The American College of Sports Medicine (ACSM) reported in their latest recommendations that there is strong evidence for the effectiveness of moderate-intensity, aerobic, and/or resistance exercise training on improving perceived physical fitness and HRQoL and reducing fatigue, anxiety, and depression. According to their recommendations cancer survivors should engage in aerobic and/or resistance exercise at least 3 times per week, with sessions of ≥ 30 minutes, for at least 8-12 weeks. It was highlighted that exercise should be supervised if possible because greater effects can be reached in supervised compared to unsupervised exercise programs.^{20,23}

While most studies focus on exercise interventions alone, multidisciplinary rehabilitation programs may better address the complex needs of cancer survivors.²⁵ Dutch Oncology Rehabilitation guidelines advocate prescription of a supervised multidisciplinary rehabilitation program for cancer survivors who experience interrelated physical and psychosocial complaints and/or fatigue.²⁶ Multidisciplinary rehabilitation commonly consists of exercise training, supplemented by other interventions aiming to improve mental health, chronic fatigue, work reintegration, and nutritional status. Since literature on multidisciplinary programs is scarce, the development of these programs is mainly based on single-intervention studies, which are then combined into one program.²⁷

Beyond supervised rehabilitation

While direct beneficial effects of exercise have been described extensively, few studies report on the long-term effects.²⁸ Kampshof et al. reported that fatigue returned to baseline levels and aerobic capacity was still “poor” in cancer survivors compared to healthy adults, 64 weeks after completing an exercise intervention.²⁹ Research showed that complaints of declined aerobic capacity, anxiety, depression, and fatigue can remain, even for years after cancer treatment.^{5,30,31} Persisting side effects can prevent cancer survivors from returning back to work, or could even lead to loss of independence in activities of daily living. It should be noted that for some

cancer survivors, treatment has to be continued for several months or years. For patients with hormone receptor-positive breast cancer, for example, hormone treatment commonly lasts five to ten years.³² As cancer survivors live longer with the consequences of cancer and are more often confronted with multimorbidity, it is crucial to prioritise their long-term health and functioning beyond the immediate post-treatment phase.

To sustain or further improve physical fitness levels that are achieved during an exercise program, patients have to stay physically active beyond these programs. It has been described extensively in the literature that regular PA has beneficial effects on several long-term side effects and disease-free survival.^{15,33–36} Therefore it is worrying that exercise programs in cancer survivors seem to have no significant effects on long-term PA levels.³⁷ Qualitative research showed that cancer survivors experience the transition from a supervised hospital-based exercise program to independent community-based exercise as “a confrontation with the real world”.²⁶ These findings stress the importance of promoting long-term PA beyond supervised exercise programs.

The role of community-based initiatives and telehealth

Extending supervised rehabilitation programs with a follow-up intervention is a potential way to increase PA maintenance beyond these programs. However, the increased pressure on the Dutch healthcare systems, asks for close collaboration with public domains and community-based initiatives when it comes to promoting a healthy lifestyle, in order to keep healthcare accessible and affordable.³⁸ Therefore, the possibility to promote long-term PA in cancer survivors with community-based initiatives and telehealth should be considered. Recent studies showed that remote coaching interventions delivered during or after a structured exercise program have the potential to support PA maintenance in cancer survivors.^{39–41} No research has been carried out yet on the effects of remote coaching following supervised rehabilitation on long-term physical fitness and patient-reported outcomes. Besides, the acceptability of remote interventions in the target population should be investigated, before successful implementation is possible.

Monitoring outcomes: the importance of aerobic capacity

Measurement tools are the key to detecting impairments in cancer survivors and referring them to adequate survivorship care. Proactive, ongoing monitoring of functional outcomes from the diagnosis of cancer would be needed to detect and treat functional impairments and to promote a healthy lifestyle throughout treatment and survivorship.⁴² In the Dutch Integrated Healthcare Agreement (in Dutch: Integraal ZorgAkkoord (IZA)), which was published in 2022 to present the current and future healthcare goals in the Netherlands, it was emphasised that improvement of lifestyle factors is important to mitigate the increasing healthcare demand and related expenses.³⁸

Physical fitness is an important outcome of a healthy lifestyle, which is also a primary focus of our work as physical therapists. Physical fitness is defined as “a set of attributes or characteristics that people have or achieve that relates to the ability to perform PA”.⁴³ An important component of physical fitness is the aerobic capacity, reflecting the integrative function of cardiovascular, pulmonary, and metabolic systems and is therefore considered a ‘clinical vital sign’ and a good reflection of overall health.⁴⁴ Moreover, aerobic capacity is inversely related to healthcare expenses and all-cause and cancer-related mortality.^{45,46} A study in veterans referred for exercise testing showed that only small increases in aerobic capacity are associated with an annual reduction in healthcare costs of roughly 6%.⁴⁶ For these reasons, it is worrying that cancer survivors experience a longstanding decline in aerobic capacity of 5–22%.^{5,47}

Accurate monitoring of aerobic capacity is important for the identification of exercise limitations, for adequate individualised training prescription, and for monitoring training progress.^{48,49} It could be questioned why other health parameters like blood pressure and heart rate are monitored throughout the patient journey of cancer and aerobic capacity is not. Aerobic capacity is quantified by the maximum amount of oxygen that can be taken in, transported, and used by the muscles to perform PA. The criterion standard to examine aerobic capacity is measuring maximum oxygen uptake (VO_2max) during a maximal incremental exercise test with respiratory gas analysis, usually referred to as a cardiopulmonary exercise test (CPET).⁵⁰

True VO_2max is achieved when oxygen consumption levels off, despite the continuation of exercise with an increasing work rate.⁵¹ However, in clinical practice, this plateau is rarely seen in nonathletic or diseased individuals. Therefore the highest oxygen uptake achieved during a maximal CPET (VO_2peak) is considered the best available index of aerobic capacity in patients with chronic diseases.⁵²

Dutch Oncology Rehabilitation guidelines recommend performing CPET for medical clearance before the start of an exercise program, in cancer survivors with an increased cardiovascular risk, such as pre-existing cardiovascular disease, treatment with cardiotoxic chemotherapy, and chest radiation and cancer survivors with unexplained exertional complaints during exercise (e.g. dyspnoea or fatigue).²⁶ This means that CPET is not always indicated for cancer survivors before the start of an exercise program. Performing a CPET for all these survivors would not be feasible, since CPET procedures are time-consuming and require advanced equipment, trained staff and medical supervision. Therefore, accurate, non-sophisticated performance-based tests to evaluate aerobic capacity in patients who currently do not undergo a CPET would be of great added value. In the Dutch Oncology Rehabilitation guidelines, the steep ramp test (SRT) is suggested as a performance test to determine training intensity and evaluate the effects of training. The SRT is a short and practical maximal exercise test performed on a cycle ergometer with an increasing work rate of 25 Watts every 10 seconds until voluntary exhaustion. Results of previous studies indicate that the SRT is valid to estimate aerobic capacity in cancer survivors.^{53,54} In situations where performance tests are not feasible, like during a phone consultation or at the oncology day unit, self-reported questionnaires could be useful to assess aerobic capacity.⁵⁵ The Duke Activity Status Index (DASI) and Veterans Specific Activity Questionnaire (VSAQ) are self-reported questionnaires that are often used to estimate aerobic capacity in cancer survivors, but the validity of these questionnaires showed to be suboptimal.^{56,57} Recently, the FitMáx®-questionnaire (hereafter: FitMáx), was developed as a self-reported questionnaire to estimate aerobic capacity, based on the self-reported maximum capacity of walking, stair climbing, and cycling combined with simple demographic characteristics. The FitMáx showed to be valid to estimate aerobic capacity in a mixed population of patients with lung, cardiac, and oncologic diseases and athletes.⁵⁸ Albeit, for both the SRT and the FitMáx, the responsiveness to

measure change in aerobic capacity has not been studied yet, while this is an important measurement property to be able to monitor aerobic capacity during medical treatment or rehabilitation.⁵⁹

Aims and outline of this thesis

The main aim of this thesis was to monitor changes in physical fitness (i.e. aerobic capacity and muscle strength) and patient-reported outcomes (i.e. HRQoL; fatigue; anxiety and depression) during a supervised exercise program as part of multidisciplinary oncology rehabilitation, optimise the transition to independent long-term PA maintenance, and assess the validity and responsiveness of different methods to monitor aerobic capacity.

Chapter 2 describes the results of an observational study on the changes in physical fitness and patient-reported outcomes in cancer survivors participating in a 10-week supervised exercise program as part of multidisciplinary rehabilitation, which is part of usual care at the MUMC+.

Chapters 3 and 4 focus on the period after completion of the supervised rehabilitation program and aim at improving long-term PA maintenance. **Chapter 3** describes the results of a randomised controlled trial (RCT) on the effectiveness of remote coaching to optimise PA maintenance during this period and to further improve physical fitness and patient-reported outcomes. **Chapter 4** presents the results of a qualitative study with interviews about determinants of PA maintenance during this transition period and the acceptability of the remote coaching intervention.

Chapters 5 and 6 address the validity and responsiveness of two different measurement tools to monitor aerobic capacity in cancer survivors participating in supervised exercise rehabilitation. **Chapter 5** describes the validity and responsiveness of the short and practical steep ramp test, while **Chapter 6** reports on the validity and responsiveness of self-reported questionnaires to monitor aerobic capacity, including the FitMáx.

Chapter 7 provides a general discussion of the most important findings of the studies described in this thesis. After reflecting on the main findings, methodological considerations and clinical implications are discussed and recommendations for future research are given in this final chapter.

References

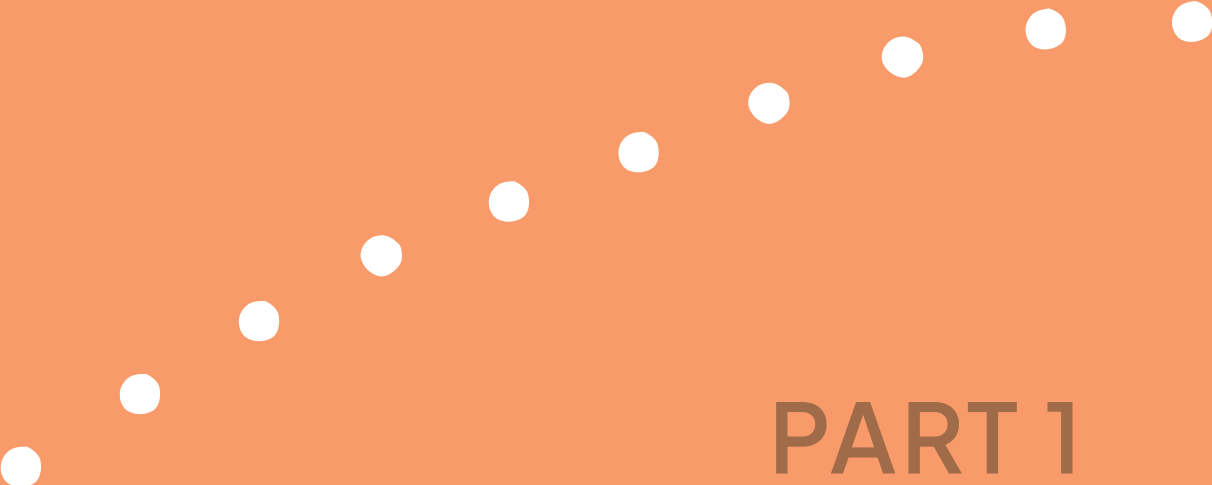
1. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. 2020.
2. National Cancer Institute. Cancer in the Netherlands - trends & prognoses until 2023. 2022.
3. Ebende CC, Y Jang Y, Escalante CP. Cancer-Related Fatigue in Cancer Survivorship. *Med Clin North Am* 2017;101(6):1085-1097.
4. Jean CY, Syrjala KL. Anxiety and depression in cancer survivors. *Medical Clinics* 2017;101(6): 1099-1113.
5. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;30(20):2530-2537.
6. Marques VA, Ferreira-Junior JB, Lemos TV, Moraes RF, Junior JRS, Alves RR et al. Effects of Chemotherapy Treatment on Muscle Strength, Quality of Life, Fatigue, and Anxiety in Women with Breast Cancer. *Int J Environ Res Public Health* 2020; 17(19):7289.
7. Nayak MG, George A, Vidyasagar MS, Mathew S, Nayak S, Nayak BS et al. Quality of Life among Cancer Patients. *Indian J Palliat Care* 2017;23(4): 445-450.
8. Duijts SF, Kieffer JM, van Muijen P, van der Beek AJ. Sustained employability and health-related quality of life in cancer survivors up to four years after diagnosis. *Acta Oncol* 2017;56(2):174-182.
9. Thraen-Borowski KM, Gennuso KP, Cadmus-Bertram L. Accelerometer-derived physical activity and sedentary time by cancer type in the United States. *PLoS One* 2017;12(8): e0182554.
10. Netherlands Cancer Registry. NKR-cijfers 2022 [cited 2023, August 4th]. Available from: <https://iknl.nl/nkr-cijfers>.
11. Statistics Netherlands (CBS). Population pyramid. Age composition in the Netherlands 2022. cited 2023, August 4th]. Available from: <https://www.cbs.nl/en-gb/visualisations/dashboard-population/population-pyramid>.
12. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca Cancer J Clin* 2018;68(6):394-424.
13. World Health Organization. Global status report on physical activity. 2022: Geneva.
14. World Health Organization. Fact Sheet Obesity and Overweight. 2021.
15. Patel AV, Friedenreich CM, Moore SC, Hayes SC, Silver JK, Campbell KL et al. American College of Sports Medicine Roundtable Report on Physical Activity, Sedentary Behaviour, and Cancer Prevention and Control. *Med Sci Sports Exerc* 2019;51(11):2391-2402.
16. Pituskin E. Cancer as a new chronic disease: Oncology nursing in the 21st Century. *Can Oncol Nurs J* 2022;32(1):87-92.
17. Kenkhuis MF, Mols F, van Roekel EH, Breedveld-Peters JJJ, Breukink SO, Janssen-Heijnen MLG et al. Longitudinal Associations of Adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Lifestyle Recommendations with Quality of Life and Symptoms in Colorectal Cancer Survivors up to 24 Months Post-Treatment. *Cancers (Basel)* 2022;14(2):417.

18. Blane DN, Lewandowska M. Living with cancer and multimorbidity: the role of primary care. *Curr Opin Support Palliat Care* 2019;13(3):213-219.
19. Corbett T, Bridges J. Multimorbidity in older adults living with and beyond cancer. *Curr Opin Support Palliat Care* 2019;13(3):220-224.
20. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
21. Shrestha A, Martin C, Burton M, Walters S, Collins K, Wyld L. Quality of life versus length of life considerations in cancer patients: A systematic literature review. *Psychooncology* 2019;28(7):1367-1380.
22. Stout NL, Alfano CM, Belter CW, Nitkin R, Cernich A, Lohmann Siegel K, Chan L. A. A Bibliometric Analysis of the Landscape of Cancer Rehabilitation Research (1992-2016). *J Natl Cancer Inst* 2018;110(8):815-824.
23. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev* 2017;52:91-104.
24. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. *J Clin Oncol* 2018;36(22):2297-2305.
25. Kudre D, Chen Z, Richard A, Cabaset S, Dehler A, Schmid M, Rohrmann S. Multidisciplinary Outpatient Cancer Rehabilitation Can Improve Cancer Patients' Physical and Psychosocial Status-a Systematic Review. *Curr Oncol Rep* 2020; 22(12):122.
26. National Cancer Institute. Dutch Cancer Rehabilitation Guidelines. 2017.
27. Mewes JC, Steuten LM, Ijzerman MJ, van Harten WH. Effectiveness of multidimensional cancer survivor rehabilitation and cost-effectiveness of cancer rehabilitation in general: a systematic review. *Oncologist* 2012; 17(12):1581-1593.
28. Jankowski CM, Steuten LM, Ijzerman MJ, van Harten WH. Searching for maintenance in exercise interventions for cancer survivors. *J Cancer Surviv* 2014;8(4):697-706.
29. Kampshoff CS, van Dongen JM, van Mechelen W, Schep G, Vreugdenhil A, Twisk JWR et al. Long-term effectiveness and cost-effectiveness of high versus low-to-moderate intensity resistance and endurance exercise interventions among cancer survivors. *J Cancer Surviv* 2018;12(3):417-429.
30. Gotze H, Friedrich M, Taubenheim S, Dietz A, Lordick F, Mehnert A.. Depression and anxiety in long-term survivors 5 and 10 years after cancer diagnosis. *Support Care Cancer* 2020;28(1):211-220.
31. Thong MSY, van Noorden CJF, Steindorf K, Arndt V.. Cancer-Related Fatigue: Causes and Current Treatment Options. *Curr Treat Options Oncol* 2020;21(2):17.
32. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol* 2016;34(6):611-635.
33. Eyl RE, Thong MSY, Carr PR, Jansen L, Koch-Gallenkamp L, Hoffmeister Met al. Physical activity and long-term fatigue among colorectal cancer survivors - a population-based prospective study. *BMC Cancer* 2020;20(1):438.

34. Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis. *JNCI Cancer Spectr* 2020;4(1):pkz080.
35. Vasbinder A, Reding KW, Wang D, Han CJ, Zaslavsky O, Langford Det al. Postdiagnosis Physical Activity: Association With Long-Term Fatigue and Sleep Disturbance in Older Adult Breast Cancer Survivors. *Clin J Oncol Nurs* 2020; 24(4):381-391.
36. Kenkhuis MF, EH VANR, Breedveld-Peters JIL, Breukink SO, Janssen-Heijnen MLG, Keulen ETPet al. Longitudinal Associations of Sedentary Behaviour and Physical Activity with Quality of Life in Colorectal Cancer Survivors. *Med Sci Sports Exerc* 2021;53(11): 2298-2308.
37. Goldschmidt S, Schmidt ME, Steindorf K. Long-term effects of exercise interventions on physical activity in breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. *Support Care Cancer* 2023;31(2):130.
38. Ministry of Health, Welfare and Sport. Integrated Healthcare Agreement. 2022.
39. Gell NM, Grover KW, Savard L, Dittus K. Outcomes of a text message, Fitbit, and coaching intervention on physical activity maintenance among cancer survivors: a randomized control pilot trial. *J Cancer Surviv* 2020;14(1):80-88.
40. Gomersall SR, Skinner TL, Winkler E, Healy GN, Eakin E, Fjeldsoe B. . Feasibility, acceptability and efficacy of a text message-enhanced clinical exercise rehabilitation intervention for increasing 'whole-of-day' activity in people living with and beyond cancer. *BMC Public Health* 2019;19(Suppl 2):542.
41. Pinto BM, Dunsiger SI, Kindred MM, Mitchell S. Peer mentoring for physical activity adoption and maintenance among breast cancer survivors: moderators of physical activity outcomes. *J Cancer Surviv* 2023; 17(4):1211-1220.
42. Stout NL, Binkley JM, Schmitz KH, Andrews K, Hayes SC, Campbell KL et al. A prospective surveillance model for rehabilitation for women with breast cancer. *Cancer* 2012;118(8 Suppl):2191-200.
43. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100(2): 126-131.
44. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BAet al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* 2016;134(24):e653-e699.
45. Han M, Qie R, Shi X, Yang Y, Lu J, Hu Fet al. Cardiorespiratory fitness and mortality from all causes, cardiovascular disease and cancer: dose-response meta-analysis of cohort studies. *Br J Sports Med* 2022;56(13):733-739.
46. Myers J, Doom R, King R, Fonda H, Chan K, Kokkinos P, Rehkopf DH. Association between cardiorespiratory fitness and health care costs: the veterans exercise testing study. in *Mayo Clinic Proceedings*. 2018. Elsevier.
47. Hurria A, Jones L, Muss HB. Cancer Treatment as an Accelerated Aging Process: Assessment, Biomarkers, and Interventions. *Am Soc Clin Oncol Educ Book* 2016;35: e516-e522.

48. Winters-Stone KM, Neil SE, Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br J Sports Med* 2014; 48(12):987-995.
49. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol* 2008;9(8):757-765.
50. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(10):1451; author reply 1451.
51. Hill AV, Lupton H. Muscular Exercise, Lactic Acid, and the Supply and Utilization of Oxygen. *QJM: An International Journal of Medicine* 1923;os-16(62):135-171.
52. Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ. The maximally attainable VO₂ during exercise in humans: the peak vs. maximum issue. *J Appl Physiol* (1985) 2003;95(5): 1901-1907.
53. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil* 2007;88(5):610-616.
54. Stuiver MM, Kampshoff CS, Persoon S, Groen W, van Mechelen W, Chinapaw MJM et al. Validation and Refinement of Prediction Models to Estimate Exercise Capacity in Cancer Survivors Using the Steep Ramp Test. *Arch Phys Med Rehabil* 2017; 98(11):2167-2173.
55. Black N. Patient reported outcome measures could help transform healthcare. *BMJ* 2013; 346:f167.
56. Li MH, Bolshinsky V, Ismail H, Ho KM, Heriot A, Riedel B.. Comparison of Duke Activity Status Index with cardiopulmonary exercise testing in cancer patients. *J Anesth* 2018;32(4): 576-584.
57. Myers J, Do D, Herbert W, Ribisl P, Froelicher VFA nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. *Am J Cardiol* 1994;73(8):591-596.
58. Meijer R, van Hooff M, Papen-Botterhuis NE, Molenaar CJL, Regis M, Timmers T et al. Estimating VO₂(peak) in 18-90 Year-Old Adults: Development and Validation of the FitMax(c)-Questionnaire. *Int J Gen Med* 2022;15:3727-3737.
59. Mokkink LB, Terwee CB, Knol DL, Stratford PW, Alonso J, Patrick DL et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. *BMC Med Res Methodol* 2010;10:22.





PART 1

Physical fitness and patient-reported outcomes
during and beyond oncology rehabilitation



CHAPTER 2

Exercise training as part of multidisciplinary
rehabilitation in cancer survivors:
an observational study on changes in physical
performance and patient-reported outcomes

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Abstract

Purpose

To describe changes in physical performance and patient-reported outcomes in cancer survivors who participated in an exercise program as part of usual-care multidisciplinary rehabilitation and the influence of training adaptations during the coronavirus-19 (COVID-19) pandemic.

Methods

In an observational cohort study, cancer survivors underwent usual-care multidisciplinary rehabilitation including a 10-week exercise program. During the COVID-19 pandemic, the exercise program was adapted with reduced training time and frequency. Mean changes and 95% confidence intervals in physical performance (peak oxygen uptake ($\text{VO}_{2\text{peak}}$), peak work rate during a steep ramp test (SRT-WRpeak), six-minute walking distance, muscle strength), and patient-reported outcomes (health-related quality of life, fatigue, anxiety and depression) were assessed between the start and the end of the exercise program. Linear regression analysis, adjusting for baseline levels of outcomes, was used to investigate differences in changes in outcomes between participants who underwent the original and the adapted program.

Results

All outcomes statistically significantly improved over time, regardless of adaptations in the exercise program. $\text{VO}_{2\text{peak}}$ increased with 9.6% and 7.7% in the original and adapted program, respectively. Significant smaller improvements were observed in SRT-WRpeak (-2.8%) and upper body muscle strength (-27.0%) after participation in the adapted compared to the original program. No significant between-group differences were observed for other outcomes.

Conclusion

Physical performance and patient-reported outcomes statistically and clinically significantly improved in cancer survivors who participated in an exercise program as part of usual-care multidisciplinary rehabilitation. Improvements of performance outcomes were smaller since the training adaptations, though only significant for SRT-WRpeak and upper body muscle strength.

Introduction

Over the last decades, ageing, improved diagnostics, and treatment modalities have led to an increased number of cancer survivors. In 2018, approximately 50 million people worldwide were living with or beyond cancer.¹ Cancer survivors are often confronted with disease- and treatment-related side effects, like fatigue, declined aerobic capacity and muscle strength, anxiety and depression, and a diminished health-related quality of life (HRQoL).²⁻⁶

Research in the field of cancer survivorship care expanded in the past decades, and growing evidence emerged for the positive effects of exercise on the aforementioned side effects.⁷⁻¹⁰ For this reason, international guidelines of the American College of Sports Medicine (ACSM) have emphasised the importance of the integration of exercise in cancer survivorship care.¹¹

While most studies focus on exercise interventions alone, multidisciplinary rehabilitation programs may better address the complex needs of patients with cancer.¹² Dutch Oncology Rehabilitation guidelines advocate prescription of a supervised, exercise-based multidisciplinary rehabilitation program for cancer survivors who experience combined physical and psychosocial problems.¹³ Multidisciplinary rehabilitation commonly contains exercise training, supplemented by a range of treatments to improve mental health, chronic fatigue, work reintegration, body composition, and nutritional intake. Recently, two systematic reviews were published about the effects of multidisciplinary oncology rehabilitation in cancer survivors. Overall, rehabilitation resulted in positive effects on physical and psychosocial state, but the effects varied across studies.^{12,14}

In recent exercise guidelines, the majority of available evidence on the efficacy of oncology rehabilitation is derived from randomised controlled trials (RCTs). RCTs have strengthened the body of proof for the efficacy of exercise in cancer rehabilitation, but have been reported to lack generalisability to the clinical setting.^{15,16} Patients have to meet pre-specified criteria (e.g. diagnosis, disease stage, age) in order to be eligible for enrolment in RCTs and have to give consent to participate. This might result in a healthier, fitter, and more motivated population, which may not be

comparable to a broader population of cancer survivors.¹¹ While RCTs have the most powerful study design to investigate the efficacy of rehabilitation in a specific population under ideal circumstances, observational studies may be more appropriate to evaluate interventions in daily practice and in more heterogeneous populations with complex, chronic diseases such as cancer.^{15,16}

In this observational study we present data about physical performance and patient-reported outcomes in cancer survivors who participated in an exercise program as part of multidisciplinary rehabilitation between February 2019 and March 2021. Due to the coronavirus-2019 (COVID-19) pandemic, social distance policies and disruption of outpatient clinic care led to changes in the content of the training and a reduction in the training time and frequency. Therefore, this study had the following objectives:

The primary objective of this study was to describe changes in aerobic capacity, muscle strength, HRQoL, fatigue, and anxiety and depression in cancer survivors who participated in a 10-week exercise program as part of usual-care multidisciplinary rehabilitation.

The secondary objective was to compare changes in outcomes between the group of participants that followed the original program and the group of participants that followed an adapted exercise program, due to COVID-19 measures.

Methods

Participants

Participants were recruited from the multidisciplinary oncology rehabilitation program at the Department of Physical Therapy of the Maastricht University Medical Centre (MUMC+) between February 2019 and March 2021. Patients participating in the program were asked for consent to use their exercise rehabilitation data. Patients who signed informed consent were included in the study. Participants were excluded if they were unable to follow the training program as intended. Patients were eligible for the program when they were ≥ 18 years, completed active medical treatment (i.e. surgery, chemotherapy, radiotherapy, stem cell transplantation), and

were suffering from physical and/or psychosocial complaints and/or chronic fatigue. Contraindications for participation in the rehabilitation program were the inability to perform basic activities of daily living and the presence of disabling comorbidities that seriously hamper physical exercise.

Study design

This study was a prospective, longitudinal observational cohort study and all data were collected during usual-care multidisciplinary oncology rehabilitation at the MUMC+. Study procedures complied with the Declaration of Helsinki and were approved by the Medical Ethics Committee of the MUMC+ with registration number 2018-0648.

Rehabilitation program

Participants completed a 10-week supervised, group-based exercise program. The exercise program consisted of two training sessions weekly, both starting with one hour of combined resistance and endurance training, followed by a 30-minute break and, subsequently, 30 minutes of varying sports activities in the gym or swimming pool. In addition, participants took part in at least one of the following interventions: a psychoeducational intervention (seven individual or group-based sessions) guided by the psychologist or the social worker; fatigue management courses (six individual or group-based sessions) guided by the occupational therapist; return-to-work counselling (three individual sessions) guided by the occupational therapist, and dietary counselling (three individual sessions) delivered by the dietician. These additional programs were provided (partly) in parallel with the exercise program. Participants completed exercise tests and questionnaires before the start of the exercise program (T=0) and in the week after completing the exercise program (T=1). Of note is that some of the other interventions were not finished yet at T=1.

Measurements

Performance outcomes

A cardiopulmonary exercise test (CPET) was performed as part of usual-care, to screen for cardiopulmonary contra-indications to exercise and to determine aerobic capacity. The CPET was conducted on a cycle

ergometer (Lode Corival; Lode BV, Groningen, The Netherlands) as described previously.¹⁷ After a warm-up phase, the work rate (WR) increased gradually according to an incremental ramp-protocol, which was determined based on the participants' self-reported physical activity level, aiming at a test duration of 8-12 minutes. The WR increased until the patient stopped cycling or pedalling frequency fell below 60 rpm. This point was defined as peak WR (CPET-WRpeak). Continuous breath-by-breath analysis was obtained using a spirometry system calibrated for respiratory gas and breathing volume measurements (Vyntus CPX, CareFusion Netherlands, the Netherlands).

CPET results were analysed by a trained researcher who was blinded for the moment of testing (T=0 or T=1), using a standardised protocol. Values of VO_2 and the respiratory exchange rate at WRpeak ($\text{VO}_{2\text{peak}}$ and RER_{peak} , respectively) were averaged over 30 seconds. An improvement in $\text{VO}_{2\text{peak}}$ of 1.0 mL/kg/min was found to be associated with a 9% risk reduction in all-cause mortality and was therefore considered a clinically relevant improvement.¹⁸ Submaximal outcomes of CPET were determined as well. The oxygen uptake (VO_2) at the ventilatory anaerobic threshold ($\text{VO}_{2\text{VAT}}$) was determined using the 'V-slope' method¹⁹ and the ventilatory equivalents method.²⁰ The VO_2 at the respiratory compensation point ($\text{VO}_{2\text{RCP}}$) was determined using the ventilatory equivalents method and the minute ventilation/carbon dioxide production (VE/VCO_2) slope.²¹ The interrater reliability for determination of $\text{VO}_{2\text{VAT}}$ and $\text{VO}_{2\text{RCP}}$ was determined previously when two researchers at MUMC+ both analysed 48 tests (partly from the current study) independently. This resulted in an intraclass correlation coefficient (ICC) of 0.95 (95% CI 0.90 ; 0.97) for determination of the $\text{VO}_{2\text{VAT}}$ and an ICC of 0.99 (95% CI 0.98 ; 0.99) for determination of the $\text{VO}_{2\text{RCP}}$, which indicates an excellent interrater reliability. The oxygen uptake efficiency slope (OUES) was derived from the relation between VO_2 and minute ventilation, using the following formula: $\text{VO}_2 = (a \times \text{Log VE}) + b$, where a is the OUES.²²

In addition, patients performed a six-minute walk test (6-MWT) and a steep ramp test (SRT). These tests also gave an indication of aerobic capacity and were performed as part of the usual-care rehabilitation program, to determine baseline training intensity. During the 6-MWT, participants were instructed to walk as many meters as possible, on a marked 44m-course,

within 6 minutes. Based on the minimal clinically important difference (MCID) of the 6MWT in adults with pathology, a change in the maximal walking distance of 30.5 m was considered clinically relevant.²³ The SRT was performed on a cycle ergometer (Lode Corival; Lode BV, Groningen, The Netherlands) as described previously.¹⁷ After a warming-up, the WR increased with 25W/10sec in a ramp-like manner, until the participant stopped cycling or pedalling frequency fell below 60 rpm. This point was defined as peak WR (SRT-WRpeak). The minimal detectable change in SRT-WRpeak was recently determined in survivors of cancer who participated in exercise-based multidisciplinary rehabilitation in MUMC+. Based on the findings of this study, an increase of 0.26W/kg in SRT-WRpeak was seen as a true improvement.¹⁷

Lower and upper body muscle strength were measured during submaximal repetition maximum (RM) tests on the leg press and chest press machine, respectively. The 5-RM was estimated for both exercises and the participant was asked to perform the maximum achievable number of repetitions up to five repetitions with this weight. When five repetitions were reached, the weight was increased and participants repeated the exercise after a 1 minute pause until they no longer reached 5 repetitions. True 1-RM values were calculated afterwards using the Brzycki equation.²⁴ In March 2020 the gym at MUMC+ was updated and the exercise machines were replaced by comparable new ones. Each participant performed strength tests at T=0 and T=1 on the same machines. A change in 1-RM chest press of 6.25 kg was considered clinically relevant, as determined in a study to the MCID of RM testing in patients with chronic obstructive pulmonary disease.²⁵

Patient-reported outcomes

HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30). Each of the 30 items has to be rated on a scale from 1 to 4 and for two items from 1 to 7. This questionnaire distinguishes 15 sub-scales. The functioning scales (physical, role, emotional, social, and cognitive functioning), the global QoL scale, and a functioning sum score (averaged across the 15 items that belong to the functioning scales) were calculated. Sub scores as well as sum scores were linearly transformed on a 100-point scale, with higher scores indicating higher levels of HRQoL.^{26,27} A change of

10 points on each subscale or the sum score, was considered clinically relevant.^{28,29}

Fatigue was assessed using the Multidimensional Fatigue Inventory-20 (MFI-20), which is a 20-item questionnaire with a five-dimensional structure (general, physical, and mental fatigue, reduced motivation, and activity). Each item is scored on a five-point Likert-scale. The sub scores range from 4 to 20, with lower scores indicating lower levels of fatigue. The sum score was calculated by adding up the sub scores.³⁰ Changes on the MFI-20 subscales that exceeded MCIDs as determined in a cohort of patients with cancer receiving radiotherapy (ranging from 3.18 to 3.80 for different subscales), were considered clinically relevant.³¹

Anxiety and depression was assessed using the 14-item Hospital Anxiety and Depression Scale (HADS). Items are scored on a 4-point scale and sub scores for anxiety and for depression range from 0 to 21, with lower scores indicating lower levels of anxiety and depression. The sum score was calculated by adding up the sub scores.³² A change of 1.7 points for each sub score was considered clinically relevant, as assessed in patients with cardiovascular disease in the study of Lemay et al.³³

Other measurements

Age, cancer type, presence of metastasis and comorbidities, treatment type, and time since treatment at T=0 were extracted from medical records. Height and weight were measured at T=0 and T=1, after which body mass index (BMI) was calculated. The training compliance (%) was calculated by dividing the number of training sessions that participants attended, by the number of planned training sessions, multiplied by 100. Indication for other interventions in the rehabilitation program and completion rates of these therapies at T=1 were reported as well.

Exercise protocol

Participants performed four strengthening exercises each session, targeting large muscle groups of the upper and lower body, and core. Resistance training consisted of three sets of 8-12 repetitions and training intensity was set at 60% of the participant's initial 1-RM. Endurance training in the first training session of the week consisted of 20 minutes of walking on a treadmill, with a walking speed of 80% of their mean speed in the

baseline 6-MWT. In the other training session, participants performed two sets of 10 minutes of interval training on a cycle ergometer, one set before and one after the resistance training program. Intervals were performed for 30 and 60 seconds at 65% and 30% of the participant's SRT-WR_{peak}, respectively.³⁴ The training load was adjusted in a personalised manner, according to the 0-10 Borg rating of perceived exertion, and a weekly increase in load was aimed for in order to reach overload. A moderate- to high exercise intensity was pursued for all training components, corresponding with a Borg score of 4-6.³⁵

COVID-19

The rehabilitation program was interrupted between March 2020 and July 2020, because all outpatient activities were cancelled in that time frame, due to COVID-19 measures. Rehabilitation data of participants who were enrolled in the exercise program prior to this period and had not finished yet, were excluded from this study because measurements at T=1 were cancelled or postponed. In July 2020, national guidelines permitted resumption of the rehabilitation program. Because of the social distancing policies, exercise training took place in smaller groups of four instead of eight patients. In order to avoid a long waiting list, the training frequency was reduced to once weekly. Because there was only one training session weekly, endurance training was changed to ten minutes of walking and ten minutes of cycling in one session. Intensity of the endurance training remained the same. Contact sports and swimming were not allowed, so patients could only perform the endurance and resistance training program. For participants who were recruited from July 2020 onwards, the frequency, time, and type of exercise training changed. However, we encouraged all participants to be physically active on other weekdays and to perform bodyweight strengthening exercises at home once to twice weekly. Online instructions for a home-based program with strengthening exercises were offered to all participants. Other interventions of the rehabilitation program took place in smaller groups as well or via phone calls.

Statistical analysis

Continuous variables were checked for normality using histograms and Q-Q plots and are presented as mean $\pm$ SD or median and interquartile ranges, as appropriate. Categorical variables are presented as frequencies (n) and

percentages (%). Performance- and patient-reported outcomes are reported for the group of participants that completed the original exercise program and the participants who completed the adapted program since COVID-19. Outcomes are reported for measurements at T=0 and at T=1. Mean changes between T=0 and T=1 in outcome variables within individuals are reported with 95% confidence intervals (CI). Mean differences (and 95% CI) in change scores between participants who underwent the original program and the adapted program were estimated using linear regression analysis, with the change scores as outcome, a group variable (indicating whether individuals followed the original or adapted exercise program) as dependent variable, and additional adjustment for the absolute values of the outcomes at T=0. Differences between changes in muscle strength were reported as percentages as well, to account for possible differences in baseline values due to the change of the exercise machine during the study. If the 95% CI did not include zero, the mean change or difference in change was considered statistically significant. MCIDs are reported when they are available in literature. Changes were considered clinically relevant when they exceeded MCIDs. Statistical analyses were performed using SPSS version 25.0.

Results

Participants

A total of 196 patients participated in the multidisciplinary oncology rehabilitation program at MUMC+ between February 2019 and March 2021. Three of them gave no informed consent for the use of their data resulting in a participation rate of 98.4%. Eight participants were excluded because they were unable to follow the exercise training as intended (i.e. because of physical impairments, absence for longer periods). This resulted in a final sample size of 185 subjects. Seventy-four and 62 participants completed the original exercise program and the adapted program since the COVID-19 pandemic, respectively. Twelve (11.0%) and 14 (18.4%) participants were unable to complete the original and the adapted exercise program due to medical or other reasons, respectively. Twenty-three out of 109 (21.1%) participants were lost to follow-up due to COVID-19 (Figure 2.1).

Of the total population, 143 participants (77.3%) were women. Mean age was 55.7 ± 11.5 years and mean BMI was 27.9 ± 5.3 kg/m². Breast cancer was the most common diagnosis (46.5%). Subjects started with the exercise program on average 4.7 ± 4.4 months after completing active medical treatment. Patient characteristics were not significantly different between groups (Table 2.1).

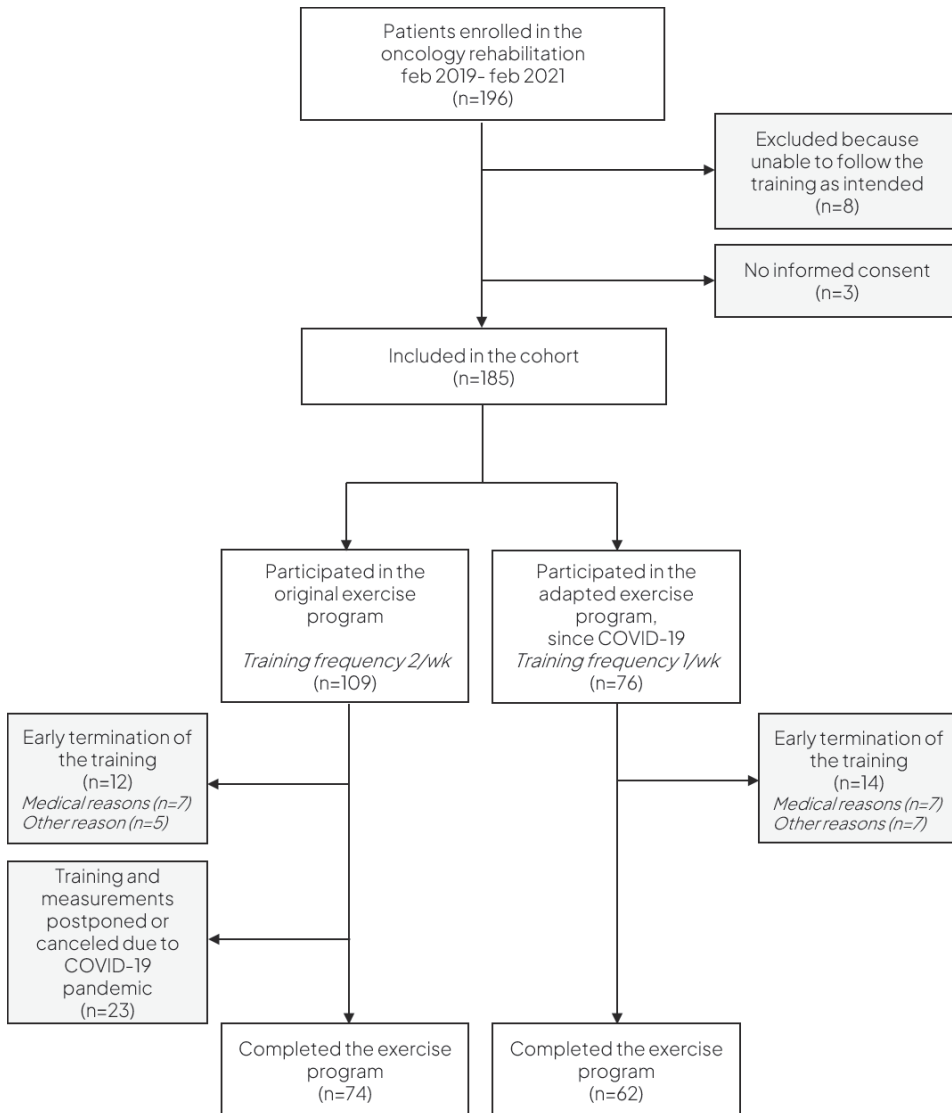


Figure 2.1 Participant flowchart. COVID-19= Coronavirus-19 pandemic.

Table 2.1. Characteristics of cancer survivors who started multidisciplinary rehabilitation overall and according to starting the rehabilitation before or after the start of the COVID-19 pandemic.

	Total population of cancer survivors n = 185	Cancer survivors who participated in the original exercise program (Training frequency 2/wk) n = 109	Cancer survivors who participated in the adapted exercise program, since the COVID-19 pandemic (Training frequency 1/wk) n=76
Sex (n,%)			
Male	42 (22.7)	27 (24.8)	15 (19.7)
Female	143 (77.3)	82 (75.2)	61 (80.3)
Age (years)	55.7 ± 11.5	56.2 ± 11.0	54.9 ± 12.2
Body height (cm)	169.0 ± 7.9	169.2 ± 8.0	168.6 ± 7.9
Body mass (kg)	79.3 ± 14.4	79.0 ± 13.8	79.8 ± 15.3
Body mass index (kg/m ²)	27.9 ± 5.3	27.6 ± 5.0	28.2 ± 5.8
Cancer type (n,%)			
Breast cancer	86 (46.5)	51 (46.8)	35 (46.1)
Lung cancer	15 (8.1)	10 (9.2)	4 (5.3)
Colorectal cancer	14 (7.6)	8 (7.3)	7 (9.2)
Lymphomas	9 (4.9)	5 (4.6)	4 (5.3)
Leukaemia	9 (4.9)	3 (2.8)	6 (7.9)
Cervix	9 (4.9)	5 (4.6)	4 (5.3)
Prostate	7 (3.8)	4 (3.9)	3 (3.7)
Other	36 (19.5)	27 (24.8)	16 (21.1)
Metastasis (n, %)			
Lymphatic metastasis	38 (20.5)	18 (16.5)	20 (26.3)
Distant metastasis	16 (8.6)	11 (10.1)	5 (6.6)
No metastasis	131 (70.8)	80 (73.4)	51 (67.1)
Treatment (n,%) ^a			
Surgery	138 (74.6)	82 (75.2)	56 (73.7)
Chemotherapy	121 (65.4)	65 (59.6)	56 (73.7)
Radiotherapy	100 (54.1)	47 (43.1)	38 (50.0)
Hormone therapy	57 (30.8)	33 (30.3)	24 (31.5)
Immunotherapy	25 (13.5)	9 (8.3)	16 (21.1)
Stem cell transplantation	8 (4.3)	3 (2.8)	5 (6.6)
Time since treatment (months)	4.7 ± 4.4	4.9 ± 4.9	4.4 ± 3.6
Comorbidity (n,%) ^b			
Cardiovascular	45 (24.3)	20 (26.3)	25 (22.9)
Respiratory	15 (8.1)	8 (7.3)	7 (9.2)
Diabetes	8 (4.3)	6 (5.5)	2 (2.6)

Values are presented as n (%) for categorical variables and as mean ± SD for continuous variables. ^a Sums of percentages are higher than 100% because participants received more than one type of treatment; ^b Sums of percentages are less than 100% because not all participants were suffering from comorbidities.

Rehabilitation program

The training compliance rate was 93.7 ± 7.7% and 91.37 ± 11.8% in participants who completed the original and the adapted program,

respectively. The percentage of indication for other interventions and their completion rates at T=1 did not differ notably between the groups, but the other interventions were often not completed yet at T=1 (Table 2.2).

Table 2.2 Participation of cancer survivors undergoing multidisciplinary rehabilitation in other interventions than the exercise intervention.

Other interventions (n, %)	Cancer survivors who participated in the original exercise program (Training frequency 2/wk) n=74	Cancer survivors who participated in the adapted exercise program, since the COVID-19 pandemic (Training frequency 1/wk) n=62
Indicated		
completed		
Psychology	58 (78.4)	50 (80.6)
Completed module at T=1 ^a	14 (24.1)	11 (22.9)
Occupational therapy fatigue	57 (77.0)	42 (67.8)
Completed module at T=1 ^a	8 (14.0)	7 (16.7)
Occupational therapy return to work	36 (48.7)	32 (51.8)
Completed module at T=1 ^a	5 (13.9)	4 (12.5)
Dietetics	12 (16.2)	10 (16.1)
Completed module at T=1 ^a	8 (66.7)	2 (0.2)

Data is presented only for participants who completed the exercise training. The frequency and percentage (n, %) of participants that were indicated for an intervention are presented. Of these participants that were indicated for the module, the frequency and percentage (n, %) of participants that completed the module at the end of the exercise program (T=1) is presented. 2/wk= twice weekly, 1/wk= once weekly. ^a Note that this was the status of completion of the intervention at T=1 and that in many instances the interventions were still ongoing.

Changes in physical performance and patient-reported outcomes

All measures of aerobic capacity and muscle strength improved statistically and clinically significantly after 10 weeks of exercise training in both groups. An increase of 1.9 mL/kg/min (9.6%) and 1.4 mL/kg/min (7.2%) in VO₂peak was observed after participation in the original and the adapted program, respectively (Table 2.3). Patient-reported outcomes for HRQoL, fatigue, and anxiety and depression improved statistically significantly after 10 weeks of exercise training, both before and after the changes in the program due to COVID-19. Clinically relevant improvements in HRQoL were reached in four out of six subscales of the EORTC-QLQ-C30 in the original program and five out of six subscales in the adapted program. A clinically relevant decrease in general and physical fatigue on the MFI was observed for both groups. Clinical relevant improvements on the HADS were seen only in the depression subscale before the adaptations in the program and in the anxiety and the depression scale after the adaptations (Table 2.4).

Table 2.3. Changes in mean outcomes of performance tests within groups and differences in changes in outcomes between the group of cancer survivors that participated in the original exercise program as part of multidisciplinary rehabilitation and the group of cancer survivors that participated in the adapted exercise program since COVID-19.

	MCID ^a	Cancer survivors who participated in the original exercise program (Training frequency 2/wk)				Cancer survivors who participated in the adapted exercise program, since the COVID-19 pandemic (Training frequency 1/wk)				Difference between groups (adapted program- original program) corrected for baseline values	
		T=0	T=1	Change Absolute %	95% CI	T=0	T=1	Change Absolute %	95% CI	Difference	95% CI
Aerobic capacity											
CPEP											
VO ₂ peak (mL/kg/min) ¹⁸	1.0	n=65 19.8 ± 5.2	21.7 ± 6.2	1.9 19.6%	1.3 ; 2.5*	n=57 19.5 ± 6.0	20.9 ± 5.9	1.4 7.2%	0.8 ; 1.9*	-0.5	-0.3 ; 1.3
WRpeak (W/kg)	N.A.	1.7 ± 0.6	1.9 ± 0.7	0.2 11.8%	0.1 ; 0.2*	1.6 ± 0.6	1.7 ± 0.7	0.1 6.3%	0.1 ; 0.2*	-0.1	-0.1 ; 0.0
RERpeak		1.16 ± 0.10	1.18 ± 0.10			1.15 ± 0.10	1.15 ± 0.11				
VO ₂ AT (mL/kg/min)	N.A.	11.7 ± 2.5	13.3 ± 3.3	1.6 13.7%	1.1 ; 2.2*	12.1 ± 3.0	13.8 ± 3.4	1.6 13.2%	1.1 ; 2.2*	0.0	-0.8 ; 0.8
OUES (/kg)	N.A.	22.7 ± 5.4	24.1 ± 6.1	1.4 6.2%	0.7 ; 2.1*	22.5 ± 6.6	23.6 ± 6.3	1.2 5.3%	0.4 ; 1.9*	-0.3	-1.3 ; 0.7
RCP reached ^b		48 (44.4)				36 (46.8)					
VO ₂ RCP (mL/kg/min)	N.A.	18.7 ± 4.3	20.8 ± 4.9	2.1 11.2%	1.5 ; 2.7*	19.0 ± 5.4	20.5 ± 5.6	1.4 7.4%	0.7 ; 2.2*	-0.7	-1.6 ; 0.3
SRT WRpeak (W/kg) ¹⁷	0.26	n=63 3.12 ± 0.92	3.48 ± 0.96	0.36 11.5%	0.28 ; 0.44*	n=55 3.02 ± 0.88	3.25 ± 0.88	0.23 7.6%	0.14 ; 0.32*	-0.13	-0.25 ; -0.02*
6-MWT (m) ²³	30.5	n=71 514 ± 104	577 ± 101	63 12.3%	51 ; 75*	n=58 515 ± 92	564 ± 104	49 9.5%	36 ; 63*	-14	-31 ; 4
Muscle strength ^c											
1- RM leg press (kg)	N.A.	n=71 86.3 ± 22.8	118.6 ± 35.1	32.3 37.4%	26.6 ; 38.0*	n=55 108.2 ± 29.2	137.0 ± 33.8	28.8 26.6%	22.8 ; 34.9*	-3.2 -10.8%	-12.3 ; 5.8 -2.9% ; 20.4%
1-RM chest press (kg) ²⁵	6.25	n=67 24.1 ± 11.3	35.8 ± 14.6	11.7 48.5%	9.7 ; 13.7*	n=54 27.0 ± 11.2	32.7 ± 11.8	5.8 21.5%	3.8 ; 7.7*	-6.0 -27.0%	-8.7 ; -3.0* -50.2% ; -9.2%*

Means ±SD were presented for both groups and changes within groups, with corresponding 95% confidence intervals (CI). Differences in change scores between groups were reported in the last column with 95% CI, corrected for baseline values, which were calculated using linear regression; *statistically significant. †clinically relevant. ‡Minimal clinically important differences are provided when they have been determined and reported in previous studies, as described in the methods section. References are provided in the first column of the table; † Frequencies and percentages of participants that reached RCP at both tests (T=0 and T=1) were reported, with corresponding values. Changes in outcomes were compared between both groups. ‡Differences in change scores between groups, with corresponding 95% CI are given in absolute numbers and | percentages, to account for baseline differences due to the usage of different exercise machines. MCID= minimal clinically important difference, CPEP= cardiopulmonary exercise test, VO₂peak= peak oxygen uptake, WRpeak = peak work rate, RERpeak= peak expiratory exchange rate, VO₂AT= oxygen uptake at anaerobic threshold, VO₂RCP= oxygen uptake at respiratory compensation point, OUES= oxygen uptake efficiency slope, SRT= steep ramp test, 6-MWT= six minute walking test, 1-RM= one-repetition maximum, 2/wk= twice weekly, 1/wk= once weekly, MCID= Minimal clinically important difference, N.A.= data not available.

Table 2.4. Changes in mean outcomes of patient-reported outcomes within groups and differences in changes in outcomes between the group of cancer survivors that participated in the original exercise program as part of multidisciplinary rehabilitation and the group of cancer survivors that participated in the adapted exercise program since COVID-19.

MCID	Cancer survivors who participated in the original exercise program (Training frequency 2/wk)				Cancer survivors who participated in the adapted exercise program since the COVID-19 pandemic (Training frequency 1/wk)				Difference between groups (adapted program – original program) corrected for baseline values	
	T=0	T=1	Change	95% CI	T=0	T=1	Change	95% CI	Difference	95% CI
Quality of life (EORTC-QLQ-C30) ^{28,29}										
Global QoL	56.86 ± 16.15	71.10 ± 16.09	14.24†	9.7; 18.8*	57.45 ± 16.23	68.79 ± 18.76	11.34†	6.6; 16.1*	-2.84	-8.63; 2.95
Physical functioning	72.04 ± 15.59	83.83 ± 12.26	11.40†	8.2; 14.6*	70.33 ± 18.67	83.83 ± 12.26	13.50†	8.8; 18.2*	1.45	-2.84; 5.74
Role functioning	55.28 ± 25.00	70.43 ± 20.56	15.16†	9.4; 20.9*	52.13 ± 26.83	74.82 ± 22.75	22.70†	15.5; 29.9*	5.42	-1.57; 12.41
Emotional functioning	63.98 ± 26.69	73.39 ± 23.80	9.40	3.7; 15.0*	61.35 ± 21.73	78.55 ± 21.73	17.20†	11.0; 23.4*	6.42	-13.18; 0.35
Cognitive functioning	62.26 ± 28.30	69.08 ± 25.93	6.80	0.9; 12.7*	62.41 ± 28.12	72.34 ± 23.90	9.93	3.7; 16.2*	3.17	-4.14; 10.49
Social functioning	59.41 ± 24.82	79.04 ± 26.98	19.63†	12.7; 26.5*	62.06 ± 29.01	78.72 ± 22.44	16.67†	10.1; 23.3*	-1.62	-9.88; 6.64
Sum score functioning	62.60 ± 17.86	75.07 ± 17.86	12.48†	8.5; 16.5*	61.65 ± 18.51	77.65 ± 14.84	16.00†	12.2; 19.8*	3.14	-1.76; 8.03
Fatigue (MFI) ³¹										
General fatigue	16 ± 3	12 ± 4	-3†	-4; -3*	16 ± 3	12 ± 4	-4†	-5; -3*	0	-2; 1
Physical fatigue	16 ± 3	10 ± 4	-6†	-7; -4*	15 ± 4	10 ± 5	-5†	-7; -4*	0	-1; 2
Reduced motivation	11 ± 4	9 ± 4	-2	-3; -2*	12 ± 4	9 ± 4	-3	-4; -2*	0	-1; 1
Reduced activity	14 ± 4	11 ± 4	-3	-4; -2*	14 ± 4	11 ± 4	-4†	-5; -3*	0	-2; 1
Mental fatigue	13 ± 4	12 ± 5	-1	-2; 0*	13 ± 5	12 ± 5	-1	-3; 0*	0	-2; 1
Sum score	69 ± 15	54 ± 17	-15	-19; -12*	71 ± 12	54 ± 17	-17	-22; -12*	-1	-7; 4
Anxiety and depression (HADS) ³³										
Anxiety	8 ± 5	7 ± 4	-1	-2; 0*	9 ± 4	7 ± 4	-2†	-3; -1*	0	-2; 1
Depression	7 ± 5	5 ± 4	-2†	-3; -1*	7 ± 4	5 ± 5	-2†	-3; -1*	0	-1; 2
Sum score	15 ± 9	12 ± 8	-4	-5; -2*	16 ± 7	12 ± 8	-4	-6; -2*	0	-2; 2

Means ± SD were presented for both groups and changes within groups, with corresponding 95% confidence intervals (CI). *statistically significant. †clinically relevant. Changes in outcomes were compared between both groups. Differences in change scores between groups were reported in the last column with 95% CI, corrected for baseline values, which were calculated using linear regression. ^aMinimal clinically important differences are provided when they have been determined and reported in previous studies, as described in the methods section. References are provided in the first column of the table. MCID= Minimal clinically important difference, EORTC-QLQ-C30= European Organization for Research and Treatment for Cancer Quality of Life Questionnaire, MFI= Multidimensional Fatigue Inventory, HADS= Hospital Anxiety and Depression score, 2/wk= twice weekly, 1/wk= once weekly.

The influence of training adaptations

For nearly all performance outcomes, changes over time were more pronounced before the adaptations in the program, albeit only statistically significantly different for SRT-WRpeak and upper body strength. Mean upper body strength improved with 48.5% in participants who took part in the original program and with 21.5% in participants who took part in the adapted program. Mean SRT-WRpeak improved with 0.36 W/kg (CI 0.28 ; 0.44) or 11.5% in participants in the original program and 0.23 (CI 0.14 ; 0.32) W/kg or 7.6% in participants in the adapted program since COVID-19 (Table 2.3). In contrast with results of the performance tests, improvements in patient-reported outcomes were not different between the groups that participated before or since training adaptations (Table 2.4).

Discussion

The results of this study showed significant improvements in aerobic capacity, muscle strength, HRQoL, fatigue, anxiety and depression in cancer survivors following a 10-week exercise program as part of usual-care multidisciplinary oncology rehabilitation. Changes were clinically relevant for nearly all outcomes, MCIDs were not available in literature for 1-RM leg press, submaximal outcomes of CPET, and for the sum score of the HADS. For SRT-WRpeak, only the minimal detectable change was available, which was therefore used to compare our study results with. A significant and clinically relevant improvement in $\text{VO}_{2\text{peak}}$ of 1.9 mL/kg/min and 1.4 mL/kg/min was seen after participation in the original program and the adapted program since COVID-19, respectively. In a meta-analysis by Scott et al. on the effects of exercise therapy on aerobic capacity in cancer survivors, a larger improvement of 2.8 mL/kg/min (CI weighted mean difference 1.58 ; 2.67 mL/kg/min in mean $\text{VO}_{2\text{peak}}$ was observed.⁹ Current guidelines of ACSM prescribe an 8-12 week combined aerobic and resistance exercise program with moderate intensity three times weekly to improve physical function.¹¹ The lower improvements in $\text{VO}_{2\text{peak}}$ found in the current study might be explained by a lower training frequency. Moreover, the moderate-to-high training intensity prescribed in the current study, was potentially not always reached due to limited adherence of training intensity. Finally, the training intensity in the current study was based on baseline performance tests and perceived exertion. Training frequency,

type, and time were equal for all participants and could be more personalised in the future.

Another plausible explanation for this inconsistency is the fact that Scott et al. only included RCTs in the meta-analysis, which might have resulted in a fitter population.^{15,16} Besides, this meta-analysis focused on the effects of exercise alone, while the current study investigated the effects of exercise as part of multidisciplinary rehabilitation, in patients with more complex care needs. Surprisingly, a systematic review of Dennett et al. showed no significant effects for supervised exercise-based, multidisciplinary rehabilitation on VO_2peak , which was attributed to issues with exercise prescriptions, which are often not well-reported in trials.¹⁴ In both reviews a large heterogeneity between studies was seen.

In our study, a significant improvement in HRQoL was seen after participation in the original program (sum score EORTC-QLQ-C30 +12.48) and the adapted program (sum score EORTC-QLQ-C30 +16.00). Comparable improvements were seen in a study on the effectiveness of a 12-week, multidisciplinary rehabilitation program in breast cancer patients (sum score EORTC-QLQ-C30 +11.67).³⁶ However, since most of our participants did not yet complete the other interventions at T=1, improvements in patient-reported outcomes probably could have been larger. Studies on oncology rehabilitation vary a lot in content, duration, and timing of the programs and in reported outcome measures. Therefore, a more extensive comparison of our study results with existing literature was not possible.

In this study, we also compared changes in outcomes between participants who exercised twice weekly in the original program and participants who exercised once weekly due to changes in the program since the COVID-19 pandemic. Significant between-group differences were observed for SRT-WRpeak and upper body muscle strength, with larger improvements for the group that participated in the original program. This is not surprising, because participants in this group attended the exercise training twice weekly. When looking at changes in the other performance outcomes, non-significant differences were seen between groups, with larger improvements for the group in the original program. Attention for habitual physical activity guidelines may have increased when training frequency and

time were diminished since COVID-19. Consequently, participants may have been more active outside the training program since the training adaptations, which could have reduced the expected difference in training improvements. No significant between-group differences were seen for patient-reported outcomes. Unexpectedly, improvements in HRQoL did not decrease under the circumstances of the COVID-19 pandemic (e.g. social isolation, anxiety). This could have been due to a 'response shift', referring to changes in internal standards and values during a crisis.³⁷ This study was not originally designed to investigate the differences between groups, therefore caution is warranted when drawing conclusions from this study based on significance testing alone.

A strength of this study was the observational design and the fact that data was collected during daily practice. The results might give a more realistic reflection of the physical and psychosocial changes after an oncology rehabilitation program, when compared to RCTs with strict inclusion criteria, in an experimental setting.^{15,16} Another strength was the fact that this study investigated a multidisciplinary rehabilitation program, which is best suited in this population with complex care needs, but has not often been studied before. Furthermore, data on different outcome measures were collected, covering not only physical but also psychosocial issues and fatigue. The observational design was not only a strength, but also a limitation of this study, because it is more challenging to draw firm conclusions about the changes in outcomes without a control group and random group assignment. It is likely that the natural course of improvement in physical performance and patient-reported outcomes after cancer treatment has played a role in the observed changes in outcomes over time. However, in the meta-analysis of Scott et al. a negligible mean improvement in VO_2peak of 0.2 mL/kg/min was seen in patients with cancer who received no exercise intervention. The fact that participants took part in interventions other than the exercise training during this study, could be seen as a limitation as well. Although patient-reported outcomes may have been influenced by other interventions than the exercise interventions alone (e.g. psychoeducational intervention, fatigue- and return-to-work counselling), these interventions were less likely to have influenced performance outcomes since they did not contain exercise elements. Further of note is that this study was aimed at investigating cancer patients with both physical and psychosocial

complaints and/or chronic fatigue. Therefore, the findings of the current study cannot be generalised to all cancer survivors.

Conclusion

The results of this study indicate that cancer survivors with both physical and psychosocial complaints, significantly improve in aerobic capacity, muscle strength, HRQoL, fatigue, anxiety and depression during a 10-week supervised, group-based exercise program as part of usual-care multidisciplinary oncology rehabilitation. Reductions in frequency, time, and type of training during the COVID-19 pandemic still resulted in significant improvements of all outcomes. However, improvements of most performance outcomes appeared to be smaller since the training adaptations, though only significant for SRT-WRpeak and upper body strength.

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References

1. World Health Organization., WHO report on cancer: setting priorities, investing wisely and providing care for all. 2020.
2. Jones, LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;30(20):2530-2537.
3. Nayak MG, George A, Vidyasagar MS, Mathew S, Nayak S, Nayak BS, et al. Quality of Life among Cancer Patients. *Indian J Palliat Care* 2017;23(4):445-450.
4. Ebede CC, Jang Y, Escalante CP. Cancer-Related Fatigue in Cancer Survivorship. *Med Clin North Am* 2017;101(6):1085-1097.
5. Jean CY, Syrjala KL. Anxiety and depression in cancer survivors. *Medical Clinics* 2017; 101(6):1099-1113.
6. Marques VA, Ferreira-Junior JB, Lemos TV, Moraes RF, Junior JRS, Alves RR, et al. Effects of Chemotherapy Treatment on Muscle Strength, Quality of Life, Fatigue, and Anxiety in Women with Breast Cancer. *Int J Environ Res Public Health* 2020;17(19):7289.
7. Stout NL, Alfano CM, Belter CW, Nitkin R, Cernich A, Lohmann Siegel K et al., A Bibliometric Analysis of the Landscape of Cancer Rehabilitation Research (1992-2016). *J Natl Cancer Inst* 2018;110(8):815-824.
8. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev* 2017;52:91-104
9. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al. Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol* 2018;36(22):2297-2305.
10. Campbell KL, Winters-Stone KM, Patel AV, Gerber LH, Matthews CE, May AM, et al. An Executive Summary of Reports From an International Multidisciplinary Roundtable on Exercise and Cancer: Evidence, Guidelines, and Implementation. *Rehabilitation Oncology* 2019;37(4):144-152.
11. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
12. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Multidisciplinary Outpatient Cancer Rehabilitation Can Improve Cancer Patients' Physical and Psychosocial Status-a Systematic Review. *Curr Oncol Rep* 2020;22(12):122.
13. National Cancer Institute. Dutch Cancer Rehabilitation Guidelines. 2017.
14. Dennett AM, Sarkies M, Shields N, Peiris CL, Williams C, Taylor NF, et al. Multidisciplinary, exercise-based oncology rehabilitation programs improve patient outcomes but their effects on healthcare service-level outcomes remain uncertain: a systematic review. *J Physiother* 2021;67(1):12-26.
15. Faraoni, D, Schaefer ST, Randomised controlled trials vs. observational studies: why not just live together? *BMC Anesthesiol* 2016;16(1):102.
16. Ligthelm RJ, Borzi V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. *Clin Ther* 2007;29 Spec No: 1284-1292.
17. Weemaes ATR, Beelen M, Bongers BC, Weijenberg MP, Lenssen AF. Criterion validity and responsiveness of the steep ramp test to evaluate aerobic capacity in survivors of cancer participating in a supervised exercise rehabilitation program. *Arch Phys Med Rehabil* 2021;102(11):2150-2156.
18. Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term change in cardiorespiratory fitness and all-cause mortality: A population-based follow-up study. *Mayo Clin Proc* 2016;91(9):1183-1188.
19. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* (1985), 1986;60(6):2020-2027.

20. Reinhard U, Muller PH, Schmulling RM. Determination of anaerobic threshold by the ventilation equivalent in normal individuals. *Respiration* 1979;38(1):36–42.
21. Simonton CA, Higginbotham MB, Cobb FR. The ventilatory threshold: quantitative analysis of reproducibility and relation to arterial lactate concentration in normal subjects and in patients with chronic congestive heart failure. *Am J Cardiol* 1988;62(1):100–107.
22. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996;28(6):1567–1572.
23. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017; 23(2):377–381.
24. Brzycki M. Strength testing—predicting a one-rep max from reps-to-fatigue. *Journal of Physical Education, Recreation & Dance* 1993;64(1):88–90.
25. Araújo Oliveira AL, Rebelo P, Paixão C, Jácome C, Cruz J, Valente C, et al. Minimal clinically important difference using one-repetition maximum in COPD. *Eur Respir J* 2019;54(63): 1205
26. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *J Natl Cancer I* 1993;85(5):365–376.
27. Hinz A, et al. Is it useful to calculate sum scores of the quality of life questionnaire EORTC QLQ-C30? *Eur J Cancer Care (Engl)* 2012;21(5):677–683.
28. Osoba D. What has been learned from measuring health-related quality of life in clinical oncology. *Eur J Cancer* 1999;35(11):1565–1570.
29. Hinz A, et al. Quality of life in cancer patients—a comparison of inpatient, outpatient, and rehabilitation settings. *Supportive Care in Cancer* 2018;26(10):3533–3541.
30. Hinz A, Eikenkel J, Briest S, Stolzenburg JU, Papsdorf K, Singer S. Fatigue in cancer patients: comparison with the general population and prognostic factors. *Support Care Cancer* 2020;28(9):4517–4526.
31. Purcell A, et al. Determining the minimal clinically important difference criteria for the Multidimensional Fatigue Inventory in a radiotherapy population. *Supportive Care in Cancer* 2010;18(3):307–315.
32. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52(2):69–77.
33. Lemay, K.R., et al., Establishing the minimal clinically important difference for the hospital anxiety and depression scale in patients with cardiovascular disease. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2019;39(6):E6–E11.
34. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil* 2007;88(5):610–616.
35. Borg G. Borg's perceived exertion and pain scales. 1998, Champaign, IL, US: Human Kinetics. viii, 104–viii, 104.
36. Leclerc AF, Foidart-Dessalle M, Tomasella M, Coucke P, Devos M, Bruyere O, et al. Multidisciplinary rehabilitation program after breast cancer: benefits on physical function, anthropometry and quality of life. *Eur J Phys Rehabil Med* 2017;53(5):633–642.
37. Sprangers MA and Schwartz CE, Integrating response shift into health-related quality of life research: a theoretical model. *Social Science & Medicine* 1999;48(11):1507–1515.



CHAPTER 3

Effects of remote coaching following supervised exercise oncology rehabilitation on physical activity levels, physical fitness, and patient-reported outcomes: a randomised controlled trial

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Abstract

Background

Studies have shown that cancer survivors experience difficulties maintaining physical activity (PA) levels after participation in a supervised exercise rehabilitation program. This study aimed to assess the effectiveness of a six-month remote coaching intervention, following a supervised exercise oncology rehabilitation program on maintenance of PA levels, and improvement of aerobic capacity, muscle strength, and patient-reported outcomes in cancer survivors.

Methods

Ninety-seven participants from a Dutch University Hospital's exercise rehabilitation program were randomised to the COACH group (n=46), receiving 6 months of remote coaching after completing the exercise program, or the CONTROL group (n=50), receiving no additional intervention. Assessment of PA levels; sedentary time; aerobic capacity; muscle strength; fatigue; health-related quality of life (HRQoL); levels of anxiety and depression; and return to work (RTW) rates were conducted at baseline (T0) and 6 months later (T1). Multiple linear regression was used for between-group statistical comparisons of all outcome measures. Mean differences at T1 were estimated with corresponding 95% confidence intervals (95%CI).

Results

No significant between-group differences were observed for all outcomes at T1. An adjusted mean difference in weekly PA of 45 minutes (95% CI -50 ; 140) was observed between the COACH group and the CONTROL group, favouring the COACH group, yet lacking statistical or clinical significance.

Conclusion

Our six-month remote coaching intervention did not notably improve PA levels; sedentary time; aerobic capacity; muscle strength; HRQoL; fatigue; anxiety and depression symptoms and RTW rates after participation in a supervised exercise oncology program. Although the participants who received coaching showed slightly higher levels of PA, these differences were not significant. More research is needed to identify patients in need for follow-up interventions following supervised exercise program and to investigate the effectiveness of remote coaching interventions in these patients.

Introduction

Cancer survivors often experience a variety of physical and psychosocial complaints, such as decreased aerobic capacity and muscle strength, fatigue, and symptoms of anxiety and depression.¹ These issues can persist for many years after completing medical treatment and can result in chronic fatigue, decreased physical activity (PA) levels, difficulties to return to work (RTW), impaired social involvement, and consequently a diminished health-related quality of life (HRQoL).^{2,3} For cancer survivors, participating in an exercise rehabilitation program is a way to increase their PA levels.

Although positive short-term effects of exercise on physical and psychosocial complaints in cancer survivors have been described extensively, few studies report on long-term effects and PA maintenance after completing a supervised exercise program.^{1,4,5} Kampshoff et al. reported that improvements in aerobic capacity and HRQoL persisted until 64 weeks after completing an exercise intervention in patients with different types of cancer, while fatigue returned to baseline level. Moreover, it turned out that levels of aerobic capacity were still 'poor' when compared to healthy adults.⁶ To further improve the health benefits that are achieved during an exercise program, patients have to stay physically active. However, it seems challenging for cancer survivors to sustain PA levels after completing a supervised exercise program. The literature indicates that short-term supervised exercise programs may be insufficient for cancer survivors to reach and sustain PA levels that meet current guidelines.⁵⁻⁸ Results of a qualitative study suggested that cancer survivors experience the transition from a supervised hospital-based exercise program to independent community-based exercise as difficult. This transition could be improved through a more structured transition, accessibility of transferable tools, sustained peer support, and ongoing monitoring.⁸

In recent randomised studies, it was shown that remote interventions, like text messages and health coaching delivered during and after a structured exercise program, can promote PA maintenance in cancer survivors.⁹⁻¹¹ However, in two of these studies^{9,10}, interventions lasted only for 8 weeks, which may be too short for habit formation¹², and long-term effects were not assessed. Besides, the effects of remote coaching on physical and psychosocial complaints were not examined in these previous studies.

Therefore, the aim of this study was to examine the efficacy of a six-month remote coaching intervention, delivered after a supervised exercise program, on maintenance of PA levels, and on improvement of aerobic capacity; muscle strength; HRQoL; fatigue; anxiety and depression symptoms and RTW rates in cancer survivors.

Methods

Design

This single-blind randomised controlled trial (RCT) recruited participants between May 2019 and December 2021, from a usual care, supervised 10-week exercise program which was part of multidisciplinary oncology rehabilitation at the Department of Physical Therapy of the Maastricht University Medical Centre (MUMC+) in the Netherlands. Patients were screened for eligibility and asked to participate during the last week of the exercise program. The content of this exercise program as part of multidisciplinary rehabilitation that was aimed at improving aerobic capacity and muscle strength has been described elsewhere.¹³ Patients who were willing to participate, gave written informed consent. After baseline measurements, participants were randomised either to the intervention group (COACH) or the control group (CONTROL) in a 1:1 ratio. The allocation sequence was generated by an independent researcher using a computer-based random number generator and was stratified for age (≤ 55 or > 55 years old) and sex in blocks of four. The allocation sequence was concealed for the researcher who enrolled participants and assigned them to groups, using sequentially numbered, sealed envelopes. Procedures of data collection were in compliance with the Declaration of Helsinki and were approved by the Medical Ethics Committee of MUMC+ with registration number 18-050. The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and was registered as NL7729 in the Dutch Trial Register (<https://trialsearch.who.int/>).

Participants

Patients were eligible to participate in this study when they were ≥ 18 years old; were suffering from physical, and/or psychosocial complaints and/or chronic fatigue, and completed active medical treatment (i.e. surgery,

chemotherapy, radiotherapy, stem cell transplantation) and a 10-week exercise program, as part of multidisciplinary oncology rehabilitation. Patients were excluded if they had insufficient understanding of the Dutch language, were in an unstable phase of disease (e.g. receiving palliative treatment), scheduled for chemotherapy, radiation, or invasive surgery in the next six months, and if they were unable to perform exercise activities without supervision (i.e. because of risk of falling or injuring).

Intervention

The six-month remote coaching intervention was delivered by a community-based sports organisation (Maastricht Sport, Municipality of Maastricht, The Netherlands) and aimed to stimulate patients to increase their PA levels. This intervention is already successfully implemented in usual care for patients who completed an exercise cardiac rehabilitation program at the MUMC+. Involved coaches had at least a bachelor's degree in Sports Science or Sports and Movement Education, were trained in behaviour change techniques, and were experienced in delivering the intervention. During a face-to-face intake assessment at the Department of Physical Therapy of the MUMC+, the coach obtained information about the subjects' personal motivation and PA preferences, using the Capability, Opportunity, and Motivation model of Behaviour (COM-B model). In this model about behaviour change, capability (physical and psychological), opportunity (physical and social), and motivation (automatic and reflective) are seen as the drivers of behaviour.¹⁴ The coaches identified facilitators and barriers for behaviour change in these three constructs using a self-developed questionnaire and adapted the coaching accordingly. The questionnaire is reported in an additional file [Appendix 3.1], with the percentage of participants who answered 'yes' and 'no'. After the intake, the program consisted of individually tailored, remote coaching. The coaching took place via phone calls or e-mails, depending on personal preferences. In the first three months, the coach approached the subjects weekly. Thereafter, the coach evaluated the individual progress, and the frequency was reduced to one contact moment per month. Attendance to the intervention was reported by the coach and adherence (%) was calculated by the researcher at the end of the study. In case of e-mail contact, participants had to respond by sending a reply e-mail to adhere to the intervention. The intervention was reported according to the Template for Intervention Description and Replication (TIDieR) guidelines.

Control group

The control group received no additional intervention. However, during the prior rehabilitation program, all patients were encouraged to reach PA levels that meet the World Health Organization (WHO) guidelines and the healthcare providers advised all patients to sustain these PA levels and informed them about possibilities for suitable community-based exercise in their neighbourhood.

Measurement procedures

Due to the nature of the intervention, it was impossible to blind participants and care providers. However, the researcher who performed data collection and data analysis was blinded until after data analysis, and validated, objective measurement tools were used in order to minimise risk of bias. Measurements of accelerometer-derived; and patient-reported PA levels; aerobic capacity; muscle strength; fatigue; HRQoL; anxiety and depression; and RTW rates were performed during the last week of the exercise rehabilitation program (T0) and were repeated six months later (T1). Patient characteristics were obtained from medical records. Self-reported PA levels before diagnosis were assessed at baseline, during short structured interviews. During this interview, participants reported the number of hours per week they walked, cycled, or performed any other kind of exercise before the diagnosis.

Accelerometer-derived PA levels

Accelerometer-derived PA levels were assessed using the validated, waterproof, thigh-mounted tri-axial MOX accelerometer (MMOXX1; Maastricht Instruments B.V.; Maastricht; the Netherlands).^{15,16} The MOX showed good test-retest reproducibility ($\kappa=0.95$) and good validity compared to direct observations ($\kappa=0.99$) for differentiating between postures (lying down/sitting and standing) and PA in a laboratory setting. Besides, the MOX has good validity for estimating time spent in the same categories in free-living conditions, compared with diary records intraclass correlation coefficient (ICC=0.98).¹⁷ The MOX accelerometer was attached to the right upper thigh, 10 cm proximal to the patella using a non-allergic plaster. Subjects wore the accelerometers 24 h/day for 7 consecutive days. With embedded software, acceleration was converted to counts per second and time could be classified as sedentary (lying down/sitting),

standing, or PA time. The primary outcome measure of this study was weekly accelerometer-derived total PA time in minutes. Weekly PA time and sedentary time were also calculated as a percentage of waking time.

Patient-reported moderate-to-vigorous intensity PA (MVPA) levels

Patient-reported moderate-to-vigorous intensity PA (MVPA) levels were monitored during the 7-day wear-time of the MOX accelerometer. Subjects were asked to report daily activities spent in MVPA of ≥ 10 minutes and wake/sleep time in a PA diary. To instruct participants, MVPA was defined as 'physical activities while standing or moving that increase the breath and heart rate (like brisk walking, cycling, gardening and exercising)'. Activities that were written down were analysed afterwards by the researcher using the compendium of PA and the total number of minutes spent in MVPA (≥ 3.0 metabolic equivalent of task, MET) was calculated.¹⁸ At T1, any consultations with a physical therapist were extracted from the diaries as well, to check for equal distribution of co-interventions between the groups.

Aerobic capacity

Aerobic capacity was examined during a maximal incremental exercise test with respiratory gas analysis, usually referred to as the cardiopulmonary exercise test (CPET). Measuring the highest amount of oxygen consumed during peak exercise ($\text{VO}_{2\text{peak}}$) during CPET is the criterion standard to evaluate aerobic capacity, has sufficient test-retest reproducibility (coefficient of variation 6%)¹⁹, and is safe and feasible in patients with cancer.²⁰ Height and weight were measured prior to the test. The CPET was performed on an electronically braked cycle ergometer (Lode Corival; Lode BV, Groningen, The Netherlands). The test consisted of a 2-minute rest period, a 3-minute warm-up phase of unloaded cycling, and a test phase with an incremental ramp protocol, adjusted to the patient's self-reported PA level, aimed at reaching a maximal effort within eight to twelve minutes. Continuous breath-by-breath analysis was obtained throughout all the phases of the test using an ergospirometry system calibrated for respiratory gas analysis measurements and volume measurements (Vyntus CPX, CareFusion Netherlands, the Netherlands). Participants were instructed to keep cycling until exhaustion, with a pedalling frequency of at least 60 rotations per minute (rpm). The protocol continued increasing until the patient stopped cycling or pedalling frequency fell below 60 rpm, despite strong verbal encouragement. Voluntary exhaustion was

considered to be achieved when participants showed clinical signs of intense effort (e.g., unsteady biking, sweating, or clear unwillingness to continue exercising). CPET results were analysed by a trained researcher who was blinded for group allocation and moment of testing (T0 or T1), using a standardised protocol. Values of oxygen uptake (VO_2) and the respiratory exchange rate at peak exercise ($\text{VO}_{2\text{peak}}$ and RER-peak , respectively) were averaged over 30s. $\text{VO}_{2\text{peak}}$ values were also converted to percentages of reference values for the Dutch general population and the number of participants that reached a $\text{VO}_{2\text{peak}}$ beneath the lower limit of normal was reported.²¹ The following submaximal CPET outcomes were determined as well, as described elsewhere: VO_2 at the ventilatory anaerobic threshold ($\text{VO}_{2\text{VAT}}$), VO_2 at the respiratory compensation point ($\text{VO}_{2\text{RCP}}$) and the oxygen uptake efficiency slope (OUES).¹³

Muscle strength

Muscle strength of the lower and upper extremities was measured during submaximal repetition maximum (RM) tests on the leg press and chest press machine. An indirect determination was used because performing a direct 1-RM test is not feasible in patients and could cause injuries. The indirect RM test was performed with a weight that allowed for a maximum of 5 repetitions. This weight was estimated and the participants were asked to perform the maximum achievable number of repetitions up to 5 repetitions. When more than 5 repetitions could be reached, the weight was increased and participants repeated the exercise after a 1-min break until they no longer reached >5 repetitions. True 1-RM values were calculated afterwards using the Brzycki equation.²² The indirect RM-test was found to have a good test-retest reproducibility in untrained persons ($\text{ICC} > 0.99$).²³

Health-related quality of life

HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30). This is a widely used questionnaire to assess HRQoL in patients with cancer, showing good psychometric properties.^{24,25} In this questionnaire, each of the 30 items has to be rated on a scale from 1 to 4 and for two items from 1 to 7. The EORTC QLQ-C30 distinguishes 15 sub-scales. The functioning scales (physical, role, emotional, social, and cognitive functioning), the global QoL scale, and a functioning sum score (averaged across the 15 items that belong to the functioning scales) were calculated

and linearly transformed on a 100-point scale. For these sub scores, higher scores indicate higher levels of HRQoL.²⁶

Fatigue

Fatigue was assessed using the Multidimensional Fatigue Inventory-20 (MFI-20), which is a validated 20-item questionnaire designed to assess fatigue in patients with cancer, using a 5-dimensional structure (general, physical and mental fatigue, reduced motivation and activity). Each item is scored on a 5-point Likert-scale. The sub scores range from 4 to 20, with lower scores indicating lower levels of fatigue. The sum score was calculated by adding up the sub scores.^{27,28}

Anxiety and depression

Anxiety and depression was assessed using the validated 14-item Hospital Anxiety and Depression Scale (HADS). Items are scored on a 4-point scale and sub scores for anxiety and for depression range from 0 to 21, with lower scores indicating lower levels of anxiety and depression. The sum score was calculated by adding up the sub scores.²⁹

Return to work

RTW was assessed during a short, structured interview. Subjects were asked whether or not they were employed before the diagnosis and for how many hours if they have reintegrated to the work process, and for how many hours/week they were working at the moment of the interview. Return to work was reported as a percentage (%) of pre-diagnosis hours of work per week.

Sample size calculation

The sample size was calculated a priori in order to be able to identify a clinically relevant difference in mean total PA time between the intervention group and the control group. A sample size which provided sufficient power (i.e. 80%) to detect a clinically relevant difference of 15min/day or 105min/week (associated with a 4% reduction in all-cause mortality)³⁰ between both groups, was pursued. When using the standard deviation (sd) of PA data from a sample of comparable patients (sd=172.46)³¹, a clinically relevant change of 105 minutes/week, and an α of 0.05 resulted in a total

sample size of $n=86$. Accounting for an expected loss-to-follow-up of 10%, we aimed to include 96 patients.

Statistical analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp). Continuous variables were checked for normality using histograms and Q-Q plots and were presented as mean $\pm$ standard deviation (sd) or as median and 1st and 3rd quartile for continuous variables, as appropriate. Categorical variables were reported as frequencies and percentages. Multiple imputation with fully conditional specification was used to impute incomplete records, to minimise potential bias from using complete cases only. The number of imputations was set to fifty, and predictive mean matching was used to draw values to be imputed. Results from inferential statistics were pooled using Rubin's rules.

Data were analysed on an intention-to-treat basis. Outcomes are reported for measurements at T0 and T1 for both groups, with mean changes from T0 to T1 and corresponding 95% confidence intervals (95% CI). Between-group differences were calculated and reported as appropriate. Multiple linear regression was used for between-group statistical comparisons of all outcomes measures. Adjusted mean differences at T1 were estimated with corresponding 95% CI. Randomisation stratification factors (age and sex) were entered in the regression models.³² In case of perceived group differences in baseline variables, these variables were entered in the regression model as well. Effect sizes (Cohen's d) of the corrected mean differences were calculated as well. Furthermore, the number of participants that showed a clinically relevant increase (≥ 105 min), remained stable (-105 min ; 105 min), or showed a clinically relevant decrease (≤ 105 min) in weekly, accelerometer-derived total PA were reported for each group, and a Pearson's chi-square test was used for between-group comparisons.

Results

Participants

Between May 2019 and December 2021, 202 patients participating in the multidisciplinary rehabilitation program of the MUMC+ were screened for

eligibility. Sixty-nine patients did not meet the inclusion criteria and 36 patients declined to participate. Reasons for exclusion and declining to participate are described in Figure 3.1. Ultimately, a total of 97 participants (48%) were included and randomly assigned to the intervention group (COACH, n=47) or the control group (CONTROL, n=50). One participant in the COACH group deceased during the course of the study and was therefore excluded from analysis (Figure 3.1).

Participants who received the intervention (n=43), completed on average 12 of the 15 intended remote coaching appointments, resulting in a mean adherence rate of 83%. Due to the measures during the coronavirus-19 (COVID-19) pandemic, the intake assessments originally scheduled for face-to-face appointments were conducted via phone calls for four participants. After the intake, seven participants chose to receive the coaching by e-mail, 34 participants received phone calls and two participants got a combination of phone calls and e-mails. The duration of the phone calls ranged from 10–20 minutes.

Outcome measures at T1 could not be collected in 8 participants in the COACH group (17%) and 5 participants in the CONTROL group (10%). Medical issues were the most common reason (46%) for drop-out. Reasons for drop-out are described in Figure 3.1. For participants who completed the outcome measurements, mean time between T0 and T1 was 27 ± 2.3 weeks in the COACH group and 27 ± 5.8 weeks in the CONTROL group. Missing outcome variables were imputed before further analysis.

Baseline characteristics are presented in Table 3.1. Breast cancer was the most common diagnosis (55%), the mean age was 54 ± 12 years and mean BMI was 27.5 ± 4.7 kg/m². Based on qualitative appraisal of the baseline characteristics, baseline accelerometer-derived weekly PA differed between the COACH and the CONTROL group. Mean weekly PA was 848 ± 256 min in the COACH group and 894 ± 256 min in the CONTROL group. Other baseline variables were balanced between both groups (Table 3.1). Therefore, baseline weekly PA was entered in the regression model as a covariate to adjust between-group analyses.

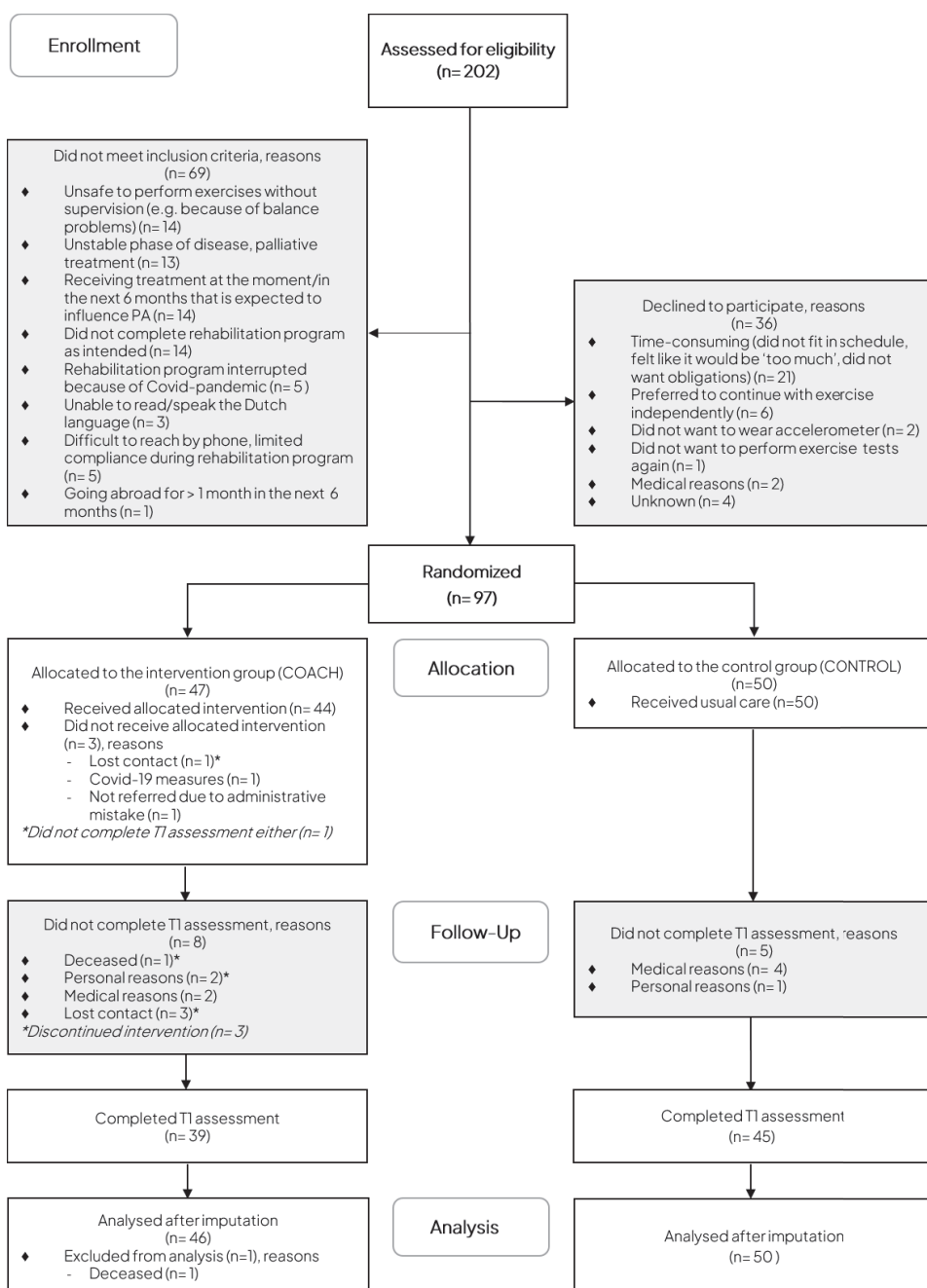


Figure 3.1. Participant flowchart. T1= outcome assessment, 6 months after the start of the study. Covid-19=Coronavirus-19.

Table 3.1. Baseline characteristics for the COACH group and CONTROL group.

	COACH group n=46	CONTROL group n=50
Sex (n,%)		
Male	9 (20%)	12 (24%)
Female	37 (80%)	38 (76%)
Age (years)	52.9 ± 10.4	55.3 ± 12.5
Body mass index (kg/m ²)	28.0 ± 5.0	26.6 ± 4.2
Cancer type (n,%)		
Breast cancer	27 (59%)	26 (52%)
Lung cancer	2 (4%)	5 (10%)
Leukaemia	2 (4%)	2 (4%)
Lymphomas	4 (9%)	1 (2%)
Colorectal cancer	3 (7%)	1 (2%)
Head- and neck cancer	-	3 (6%)
Other	8 (17%)	12 (24%)
Metastasis (n, %)		
Lymphatic metastasis	7 (16%)	17 (34%)
Distant metastasis	3 (7%)	1 (2%)
No metastasis	36 (78%)	32 (64%)
Treatment (n,%)		
Surgery	38 (83%)	41 (82%)
Chemotherapy	29 (63%)	29 (58%)
Radiotherapy	23 (50%)	28 (56%)
Hormone therapy	15 (33%)	16 (32%)
Immunotherapy	8 (17%)	7 (14%)
Stem cell transplantation	2 (4%)	1 (2%)
Time since active medical treatment (months)	7.5 ± 6.1	6.3 ± 4.0
Comorbidity (n,%)		
Cardiovascular	10 (22%)	11 (22%)
Respiratory	1 (2%)	5 (10%)
Musculoskeletal	11 (24%)	19 (38%)
Psychological	4 (9%)	7 (14%)
Self-reported exercise history before diagnosis (hours/week)	5 ± 5	6 ± 7
Employed before diagnose	38 (83%)	39 (78%)
Weekly physical activity T0 (min) ^A	848 ± 256	894 ± 256
Peak oxygen uptake T0 (mL/kg/min)	22.3 ± 6.1	22.7 ± 6.1
Quality of life (EORTC-QLQ-C30 sum score)	73.1 ± 15.6	74.6 ± 15.3
Fatigue (MFI-20 sum score)	57 ± 15	54 ± 18
Anxiety and Depression (HADS sum score)	11 ± 6	12 ± 8

Values are presented as n(%) for categorical variables and as mean ± SD for continuous variables. ^A Accelerometer-derived total physical activity (including physical activity of all intensities e.g. light, moderate and vigorous intensity). EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, MFI-20= Multidimensional Fatigue Inventory-20, HADS= Hospital Anxiety and Depression Scale, T0=Baseline.

Within-group changes

At T1, mean weekly accelerometer-derived total PA increased with +33 min (95% CI -48 ; 113) in the COACH group and decreased with -30 min (95% CI -96 ; 36) in the CONTROL group compared to levels at T0. Both within-group changes were not significant. Besides, the weekly time that participants were sedentary during waking hours decreased with -147 min (95% CI -396 ; 102) in the COACH group and increased with +62 min (95% CI -194 ; 317) in the CONTROL group, although not significant. No significant changes over time from T0 to T1 were seen either for mean values of weekly self-reported MVPA, CPET outcomes, upper and lower body muscle strength and different domains, and sum scores of HRQoL, fatigue, and anxiety and depression, in both groups. RTW increased significantly in both groups, with 29% (95%CI 16 ; 42) in the COACH group and 35% (95% CI 18 ; 51) in the CONTROL group (Table 3.2 and 3.3).

In the COACH group, 17 participants (37%) showed a clinically relevant increase (≥ 105 min) in weekly accelerometer-derived PA, 15 participants (33%) remained stable and 14 participants (30%) showed a clinically relevant decrease (≤ 105 min). In the CONTROL group, 12 participants (24%) showed a clinically relevant increase (≥ 105 min), 24 participants (48%) showed no change and 14 participants (28%) showed a clinically relevant decrease (≤ 105 min) in weekly accelerometer-derived PA. Clinically relevant changes were not statistically significantly different between groups ($p=0.58$). Individual participant changes from T0 to T1 in weekly accelerometer-derived physical activity are visualised in line graphs for both groups (Figure 3.2).

Table 3.2. Physical activity levels and performance outcomes at T0 and T1 with corresponding changes in both groups.

	COACH T0	COACH T1	COACHΔ (95% CI)	CONTROL T0	CONTROL T1	CONTROLΔ (95% CI)
Weekly PA level						
Weekly accelerometer-derived total PA(min)	848 ± 256	881 ± 268	33 (-48; 113)	894 ± 256	864 ± 253	-30 (-96; 36)
Weekly wake time (min)	6332 ± 302	6265 ± 555	-67 (-279; 146)	6308 ± 280	6298 ± 459	-9 (-206; 187)
PA as percentage of waking time (%)	13 ± 4	14 ± 4	1 (-1; 2)	14 ± 4	14 ± 4	0 (-2; 0)
Weekly accelerometer-derived sedentary wake time (min) ^A	4157 ± 615	4010 ± 819	-147 (-396; 102)	3940 ± 639	4002 ± 765	62 (-194; 317)
Sedentary wake time as percentage of waking time (%)	66 ± 9	64 ± 11	-2 (-5; 1)	62 ± 9	63 ± 11	1 (-2; 4)
Self-reported weekly MVPA (min)	591 ± 364	557 ± 400	-35 (-189; 119)	619 ± 324	589 ± 414	-30 (-171; 110)
CPET outcomes						
VO ₂ peak (mL/kg/min)	22.3 ± 6.1	22.2 ± 5.9	-0.1 (-1.2; 1.1)	22.7 ± 6.1	22.6 ± 6.5	-0.1 (-1.2; 1.0)
% predicted	71 ± 17	71 ± 17	0 (-4; 4)	75 ± 17	74 ± 18	0 (-4; 3)
RERpeak	1.18 ± 0.09	1.18 ± 0.08	0.00 (-0.02; 0.03)	1.19 ± 0.10	1.17 ± 0.09	-0.01 (-0.04; 0.00)
VO ₂ VAT (mL/kg/min)	13.5 ± 3.3	13.0 ± 4.4	-0.5 (-2.0; 0.9)	13.7 ± 3.5	13.2 ± 4.3	-0.5 (-1.7; 0.8)
VO ₂ RCP (mL/kg/min) ^B	20.5 ± 5.9	20.3 ± 5.7	0.0 (-1.4; 1.5)	21.7 ± 5.9	20.7 ± 5.9	-0.4 (-1.7; 0.9)
OUES	24.8 ± 6.8	24.6 ± 6.5	-0.2 (-1.6; 1.2)	25.3 ± 6.1	25.4 ± 6.9	0.2 (-1.1; 1.4)
Muscle Strength						
1-RM leg press (kg)	135 ± 36	133 ± 35	-2 (-11; 8)	132 ± 34	130 ± 35	-3 (-12; 7)
1-RM chest press (kg)	34 ± 13	34 ± 13	0 (-3; 3)	34 ± 13	34 ± 13	1 (-3; 2)

Means ± SD were presented for both groups and timepoints. Mean changes over time (Δ) were presented with corresponding 95% confidence intervals (95% CI).

^A Weekly time that participants were sedentary during waking hours. ^B The RCP was not always reached during the CPET tests and was not imputed in cases a test was completed correctly and RCP was not reached Group A T0: n=41, T1 n=41; Group B T0: n=37, T1 n=44. * Statistically significant. COACH= the group of participants receiving a remote coaching intervention; CONTROL= the group of participants receiving no intervention; T0=baseline; T1= follow-up. PA=physical activity, MVPA=moderate-to-vigorous physical activity, VO₂peak=peak oxygen uptake, RER=respiratory exchange rate, VO₂VAT=oxygen uptake at ventilatory anaerobic threshold, VO₂RCP= oxygen uptake at respiratory compensation point, OUES= oxygen uptake efficiency slope, 1-RM=one-repetition maximum.

Table 3.3. Patient-reported outcomes at T0 and T1 with corresponding changes in both groups.

	COACH T0	COACH T1	COACHΔ (95% CI)	CONTROL T0	CONTROL T1	CONTROLΔ (95% CI)
Quality of Life (EORTC-QLQ- C30)						
Global quality of life	69.6 ± 17.6	71.7 ± 17.9	2.1 (-4.1; 8.3)	69.3 ± 15.1	70.8 ± 19.7	1.6 (-2.6; 5.8)
Physical functioning	83.1 ± 12.1	84.3 ± 14.8	1.2 (-3.2; 5.5)	84.7 ± 12.9	84.1 ± 15.9	-0.6 (-3.9; 2.7)
Role functioning	68.4 ± 25.6	72.8 ± 26.1	4.4 (-5.4; 14.2)	72.7 ± 21.1	71.4 ± 22.4	-1.3 (-8.4; 5.9)
Emotional functioning	73.4 ± 21.9	80.6 ± 17.5	7.2 (-0.8; 15.2)	74.1 ± 23.1	70.6 ± 25.1	-3.4 (-9.8; 3.0)
Cognitive functioning	68.9 ± 25.2	75.4 ± 19.9	6.5 (-0.7; 13.7)	69.5 ± 25.0	71.3 ± 23.7	1.8 (-3.8; 7.3)
Social functioning	75.3 ± 27.8	79.6 ± 26.1	4.3 (-5.4; 14.1)	77.5 ± 24.7	75.5 ± 25.3	-2.0 (-10.6; 6.5)
Sum score	73.1 ± 15.6	77.4 ± 14.4	4.3 (-0.5; 9.1)	74.6 ± 15.3	74.0 ± 16.5	-0.7 (-4.4; 3.1)
Fatigue (MFI-20)						
General fatigue	13 ± 4	12 ± 4	-1 (-2; 1)	12 ± 4	12 ± 5	0 (-1; 1)
Physical fatigue	11 ± 4	11 ± 5	-1 (-2; 1)	10 ± 4	11 ± 5	1 (-1; 2)
Reduced motivation	10 ± 4	9 ± 4	-1 (-3; 0)	9 ± 4	10 ± 5	0 (-1; 1)
Reduced activity	11 ± 4	10 ± 4	-1 (-2; 0)	11 ± 4	11 ± 5	0 (-1; 1)
Mental fatigue	12 ± 4	11 ± 4	-1 (-3; 0)	12 ± 4	11 ± 5	0 (-1; 1)
Sum score	57 ± 15	53 ± 16	-5 (-10; 0)	54 ± 18	55 ± 20	0 (-4; 5)
Anxiety and depression (HADS)						
Anxiety	7 ± 4	6 ± 4	-1 (-2; 1)	7 ± 4	6 ± 4	0 (-1; 0)
Depression	5 ± 4	4 ± 3	-1 (-2; 1)	5 ± 4	5 ± 4	0 (-1; 1)
Sum score	11 ± 6	10 ± 6	-1 (-3; 1)	12 ± 8	11 ± 8	-1 (-2; 1)
Return to work ^A						
No, n(%)	20 (51%)	8 (24%)	-	17 (45%)	10 (29%)	-
Yes, n(%)	19 (49%)	25 (76%)	-	21 (55%)	24 (71%)	-
Hours returned (%) [*]	22 ± 32	51 ± 43	29 (16; 42*)	23 ± 29	58 ± 49	35 (18; 51*)

Means ± SD were presented for both groups and timepoints. Mean changes over time (Δ) were presented with corresponding 95% confidence intervals (95% CI)^A. RTW was not imputed for participants who were not employed (anytime) before the diagnosis of cancer Group A n=38; Group B n=39). * Statistically significant. COACH= the group of participants receiving a remote coaching intervention; CONTROL= the group of participants receiving no intervention; T0=baseline; T1= follow-up. EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, MFI-20= Multidimensional Fatigue Inventory-20, HADS= Hospital Anxiety and Depression Scale.

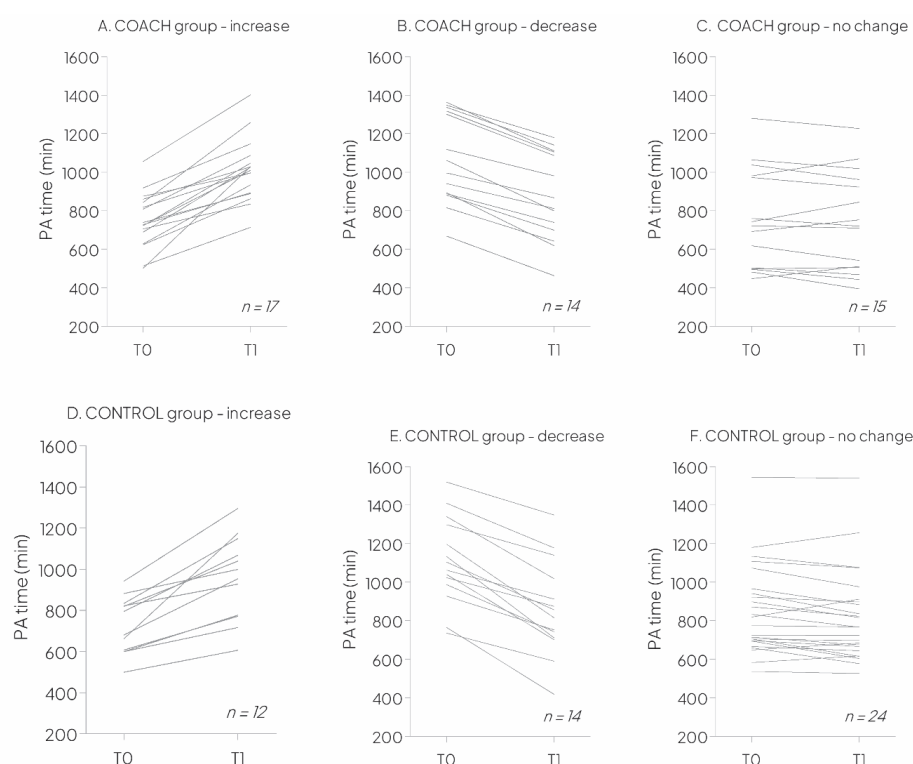


Figure 3.2. Individual participant changes from T0 to T1 in weekly accelerometer-derived physical activity (min) for participants in the COACH group who showed a relevant increase (A), decrease (B) or no change (C) in weekly physical activity, and for participants in the CONTROL group who showed a relevant increase (D), decrease (E) or no change (F) in weekly physical activity. Values of some patients are based on mean of multiple imputed values. COACH= the group of participants receiving a remote coaching intervention; CONTROL= the group of participants receiving no intervention, T0= baseline assessment, start of the study; T1= outcome assessment, 6 months after the start of the study.

Between-group differences

After adjusting for sex, age, and baseline weekly accelerometer-derived total PA, no significant between-group differences were seen at T1 for weekly accelerometer-derived total PA, VO_{2peak} , 1-RM leg press, 1-RM chest press, and sum scores for HRQoL, fatigue, anxiety and depression and RTW (Table 3.3). Ten participants in the COACH group (22%) and ten participants in the CONTROL group (20%) went to the physical therapist during the study period, so co-interventions were equally divided between groups. At T1, weekly accelerometer-derived total PA was on average

881 ± 268 min in the COACH group and 864 ± 253 min in the CONTROL group. For both groups, this was equal to 14 ± 4% of their waking time. An adjusted mean difference of 45 min (95%CI -50 ; 140, $p=0.35$) was seen for the COACH group minus the CONTROL group at T1, indicating slightly higher levels of PA in the COACH group, although not statistically significant. This was confirmed by the Cohen's effect size of $d=0.17$, indicating a small effect. Weekly sedentary time during waking hours was 4010 ± 819 min (64 ± 11%) in the COACH group and 4002 ± 765 min (63 ± 11%) in the CONTROL group, resulting in an adjusted mean difference of -36 (95%CI -389 ; 318, $p=0.84$) min per week (Table 3.4). The COACH group reached a mean VO_2 peak of 22.3 ± 6.1 (71 ± 17% of predicted), while the CONTROL group showed a mean value of 22.7 ± 6.4 (75 ± 19% of predicted) (Table 3.2). At T1, 19 participants in the COACH group (41%) and 18 participants in the CONTROL group (36%) reached a VO_2 peak beneath the lower limit of normal.²¹ A small, but non-significant effect was found for HRQoL as well, with a corrected mean difference of 4.0 points (95% CI -2.9 ; 10.0) on the EORTC-QLQ-C30, and an effect size of $d=0.26$ favouring the COACH group.

Table 3.4. Between group differences at T1 using linear regression.^A

	Mean difference ^B (95% CI)	P-value	Cohen's <i>d</i> effect size ^D
Weekly accelerometer-derived total PA (min)	45 (-50 ; 140)	0.35	0.17
Weekly accelerometer-derived sedentary wake time (min) ^C	-36 (-389 ; 318)	0.84	-0.05
Weekly self-reported weekly MVPA (min)	-16 (-190 ; 158)	0.86	-0.04
Peak oxygen uptake, VO_2 peak (mL/kg/min)	-0.7 (-2.9 ; 1.4)	0.50	-0.11
1-RM leg press (kg)	2 (-12 ; 17)	0.77	0.06
1-RM chest press (kg)	0 (-4 ; 5)	0.94	0.00
Quality of Life, EORTC-QLQ-C30 Sum score	4.0 (-2.9 ; 10.0)	0.28	0.26
Fatigue, MFI Sum score	-2 (-10 ; 6)	0.52	-0.11
Anxiety and depression, HADS Sum score	-1 (-4 ; 2)	0.42	-0.14
Return to work, percentage hours returned (%)	-7 (-29 ; 16)	0.55	-0.15

^A Corrected for gender, age, and baseline values of weekly physical activity. ^B Mean difference is = unstandardized B; COACH group minus CONTROL group. ^C Weekly time that participants were sedentary during waking hours. ^D Calculated as the corrected mean difference divided by the pooled standard deviation for both groups at T1. T1= follow-up; PA= physical activity, MVPA = moderate-to-vigorous physical activity, VO_2 peak=peak oxygen uptake 1-RM=one-repetition maximum EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, MFI-20= Multidimensional Fatigue Inventory-20, HADS= Hospital Anxiety and Depression Scale, 95% CI= 95% confidence interval.

Discussion

This study shows that extending a supervised exercise-based oncology rehabilitation program with our six-month remote coaching intervention had no significant benefits compared to no additional intervention. No significant between-group differences were seen for weekly accelerometer-derived PA levels; sedentary time and self-reported MVPA levels; aerobic capacity; upper and lower body muscle strength; quality of life; fatigue; anxiety and depression; and RTW; after six months of receiving or not receiving a remote coaching intervention. An adjusted mean difference in weekly accelerometer-derived total PA of 45 minutes was seen between the COACH group and the CONTROL group at T1, favouring the COACH group, and a small effect size of $d=0.17$, but effects were not statistically nor clinically relevant.²⁸ RTW increased significantly in both groups, while all other outcomes remained stable within both groups, six months after completing the supervised exercise program. However, non-significant within-group changes of +33 min in the COACH group and -30 min in the CONTROL group were seen in the primary outcome measure accelerometer-derived PA.

We hypothesized that the COACH group would maintain or improve PA levels, while the CONTROL group would show a decrease. However, results showed that 70% and 72% of the participants in the COACH group and CONTROL group respectively, were able to maintain or improve PA levels six months after completing supervised exercise oncology rehabilitation. No significant between-group differences were seen for the distribution of participants that showed a decrease, an increase, or no change in PA levels. The ability to maintain PA levels after a supervised rehabilitation program varied considerably across participants and was not affected by a remote coaching intervention (Figure 3.2).

At T1, participants in the COACH group had a total accelerometer-derived PA of 881 ± 268 min/week compared to 864 ± 253 min/week in the CONTROL group. For both groups, this was equal to $14 \pm 4\%$ of their waking time. Participants in the COACH group and the CONTROL group spent on average 64% and 63% of their waking time sedentary. The PA levels in the current study are comparable, but slightly higher compared to those of patients with colorectal cancer in a Dutch cohort study ($n=114$), who were

older than our population (mean age 70.0 years) and showed a physical activity time of 1.7h/day, equal to 714 min per week, measured with the MOX accelerometer.³³ In an RCT by O'Neill et al., a higher mean total PA time of 1650 min/week was found in participants with esophagogastric cancer in Ireland (n=22, mean age 61.4 years), measured with the ActiGraph accelerometer, 3 months after participating in a 12-week multidisciplinary rehabilitation program containing supervised exercise, with no significant changes over time since the end of the program.³⁴ Sweegers et al.³⁵ pooled ActiGraph accelerometer data of 1447 cancer survivors from the Netherlands, Australia, Canada, and the United states, with a mean age of 59.3 years and a median time since medical treatment of 46.6 months. They reported that participants spent on average 66% of their day sedentary, which is in accordance with the results of the current study. Total physical activity, on the other hand, was much higher in their study, with 297 min/day, or 2075min /week. This discrepancy could be partly explained by the fact that time spent in standing posture was included in PA time in their study, while this was not the case in the current study. Large differences in PA time between studies could be due to differences in the population (e.g. age, diagnosis, living area) and the use of different accelerometers. Besides, in some of the studies, participants took part in a rehabilitation program, while this was not the case in other studies.

It is difficult to further interpret the values for weekly total PA time correctly because normative values or guidelines do not exist. The WHO guideline only reports thresholds on the recommended amount of min/week spent in MVPA (PA with an intensity ≥ 3.0 METs).³⁶ In this study, we did not subdivide PA, because of a limited reproducibility of the MOX-accelerometer for estimating minutes of MVPA.¹⁷ While the recent guidelines only report thresholds on the amount of MVPA per week, the recommendation to minimise sedentary behaviour was added.³⁶ This was underpinned by the acknowledgement that replacing sedentary time with any intensity of PA (including light activity), has health benefits. However, there is still insufficient evidence to determine quantitative thresholds and specific recommendations on reducing sedentary behaviour apart from MVPA. We asked participants to keep a PA diary in order to get insight in minutes of MVPA. At T1 participants in the COACH group reported 557 ± 400 min of MVPA, while the CONTROL group reported 589 ± 414 min. These values are much higher than the WHO guidelines of 150–300 min. It can be expected

that time of MVPA was highly overestimated by the participants, as was concluded by Smith et al. in a study about self-reported PA in patients with prostate cancer.³⁷

In contrast to the findings of our study, a meta-analysis of Roberts et al. showed significant positive effects for digital interventions on PA levels in cancer survivors (mean difference in MVPA=49 min/week, 95% CI 16 ; 82). However, the included studies used self-reported PA as outcomes and high levels of heterogeneity were seen.³⁸ Gomersal et al. reported that a 12-week tailored text messaging intervention, additional to a standard-care 4-week oncology rehabilitation program had beneficial effects on sitting time and time spent in light-intensity PA, but not on MVPA, measured with the activPAL accelerometer.¹⁰ In a study of Gell et al., cancer survivors who received tailored advice from a health coach and follow-up phone calls and messages, combined with a Fitbit activity monitor for goal setting following an exercise-based rehabilitation program maintained accelerometer-derived (Actigraph) MVPA levels eight weeks later. Participants who got a Fitbit activity monitor with one-off advice only, showed a significant decline in MVPA minutes.⁹

In the current study, we also assessed aerobic capacity. Results showed that aerobic capacity remained stable from T0 to T1 in both groups, without between-group differences. At T1, participants in the COACH group reached mean a VO_{2peak} of 22.2 mL/kg/min (71% of predicted), while participants in the CONTROL group had a mean VO_{2peak} of 22.6 mL/kg/min (74% of predicted). For 41% and 36% of the participants in the COACH group and the CONTROL group respectively, these values were below the lower limit of normal.²¹ These findings confirm that a 10-week supervised rehabilitation program was not sufficient to reach normal levels of aerobic capacity and, in contrast to our hypothesis, additional remote coaching had no beneficial effects. This is worrying since aerobic capacity can be seen as a clinical vital sign and is inversely related to all-cause and cancer-related mortality.^{39,40}

Contrary to our expectations and findings of previous studies, our remote coaching intervention following supervised exercise rehabilitation did not show to be significantly effective to improve PA levels, sedentary time, physical fitness, and patient-reported outcomes. One potential

explanation is the fact that a relatively motivated group of participants was selected for this study, since they were willing to attend the supervised rehabilitation program in the first place and consented to participate in this study afterwards. These patients might have been more motivated to sustain or increase PA levels, compared to the general population of cancer survivors. This was confirmed by our data, showing that 72% of the participants in the CONTROL group, who did not receive any additional intervention after the supervised rehabilitation, was able to maintain or increase PA levels. Moreover, participants in this study were relatively young compared to the general cancer population. The mean age was comparable to other studies on exercise oncology rehabilitation, which indicates that more research is needed on targeting older cancer survivors for oncology rehabilitation.^{13,41} Potentially, the effects of remote coaching investigated in this study would have been significant if only patients in need were targeted. Harris et al. described that elderly participating in a physical activity study reported greater physical activity than the non-participants.⁴² Furthermore, the study information and the follow-up measurements may have been a stimulus for participants to sustain PA levels. Receiving information about the study might have raised the awareness for PA maintenance and the prospect of follow-up measurements potentially motivated people to stay active. Besides, participants may have increased PA during the week of the accelerometer measurement. This phenomenon is known as measurement reactivity, meaning that behaviour is likely to change when it is monitored.⁴³ However, this probably occurred in both the COACH group and the CONTROL group and did therefore not influence intervention effects. This can be confirmed by the finding that aerobic capacity remained stable over time and did not differ between groups either, since increasing PA in the week of the measurement does not influence outcomes of aerobic capacity.

Strengths of our study included the objective and accurate measurement of PA and sedentary behaviour using the MOX accelerometer and aerobic capacity using the CPET. However, more research is needed to determine thresholds for categorising intensities of PA using objective PA measurements, such as accelerometry. Furthermore, a broad spectrum of variables was collected, covering not only physical but also psychosocial outcomes and fatigue. One of the limitations was the fact that participants were recruited from a multidisciplinary rehabilitation program, suitable for

patients who experience both physical and psychosocial complaints and/or chronic fatigue. Therefore, the findings of this study are not generalisable to all cancer survivors. Besides, PA behaviour might have changed during the course of this study because of the COVID-19 pandemic. However, because of the randomised controlled design, this is unlikely to have distorted the study results. The majority of the participants completed the intervention as intended despite the COVID-19 measures. Another limitation was the fact that intervention dose and duration were equal for all participants in this study. This intervention should be optimised and personalised in the future. Important keys that play a role in PA maintenance should be taken into account when optimising the intervention. A qualitative study showed that the remote coaching intervention investigated in the current study was acceptable for cancer survivors, but added value differed between patients. For some participants, the intervention could be improved by adding face-to-face appointments. Self-efficacy, accountability, PA habits, physical complaints, and accessibility of facilities were key themes for PA maintenance and should therefore be taken into consideration when improving the intervention.⁴⁴

Future research should focus on identifying determinants (e.g. patient characteristics, medical status, social environment) that are related to PA maintenance after supervised rehabilitation. This would enable healthcare providers to monitor the patients at risk beyond the program and offer them a follow-up intervention. In addition, the content of remote coaching could be improved accordingly and tested for efficacy. Since reaching, and motivating patients through remote coaching interventions is challenging, appropriate methods to achieve this should be explored, as well as the acceptability of these interventions in the target population. Another limitation is the fact that little is known about the minimal clinically important change in PA. Future research should look into the minimal change in PA that is relevant for cancer survivors. Lastly, after optimising this remote coaching intervention, knowledge should be expanded to adjacent regions and effectiveness should be investigated at a larger scale.

Conclusion

Extending a supervised exercise oncology rehabilitation program with a six-month remote coaching intervention was not effective to improve maintenance of PA levels; aerobic capacity; muscle strength; and patient-reported outcomes in cancer survivors. However, a non-significant mean difference of 45 minutes in PA was found, favouring the group of participants that received the remote coaching intervention. More research is needed to identify patients most in need of follow-up interventions following supervised exercise programs and to investigate the effectiveness of remote coaching interventions in these patients.

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References

1. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
2. Duijts SF, Kieffer JM, van Muijen P, van der Beek AJ. Sustained employability and health-related quality of life in cancer survivors up to four years after diagnosis. *Acta Oncol* 2017;56(2):174-182.
3. Thraen-Borowski KM, Gennuso KP, Cadmus-Bertram L. Accelerometer-derived physical activity and sedentary time by cancer type in the United States. *PLoS One* 2017;12(8): e0182554.
4. Grimmett C, Corbett T, Brunet J, Shepherd J, Pinto BM, May CR, Foster C. Systematic review and meta-analysis of maintenance of physical activity behaviour change in cancer survivors. *Int J Behav Nutr Phys Act* 2019;16(1):37.
5. Spark LC, Reeves MM, Fjeldsoe BS, Eakin EG. Physical activity and/or dietary interventions in breast cancer survivors: a systematic review of the maintenance of outcomes. *J Cancer Surviv* 2013;7(1):74-82.
6. Kampshoff CS, van Dongen JM, van Mechelen W, Schep G, Vreugdenhil A, Twisk JWR et al. Long-term effectiveness and cost-effectiveness of high versus low-to-moderate intensity resistance and endurance exercise interventions among cancer survivors. *J Cancer Surviv* 2018;12(3):417-429.
7. Schmidt ME, Wiskemann J, Ulrich CM, Schneeweiss A, Steindorf K. Self-reported physical activity behaviour of breast cancer survivors during and after adjuvant therapy: 12 months follow-up of two randomized exercise intervention trials. *Acta Oncol* 2017;56(4):618-627.
8. Schmidt MLK, Ostergren P, Cormie P, Ragle AM, Sonksen J, Midtgaard J. "Kicked out into the real world": prostate cancer patients' experiences with transitioning from hospital-based supervised exercise to unsupervised exercise in the community. *Support Care Cancer* 2019;27(1):199-208.
9. Gell NM, Grover KW, Savard L, Dittus K. Outcomes of a text message, Fitbit, and coaching intervention on physical activity maintenance among cancer survivors: a randomized control pilot trial. *J Cancer Surviv* 2020;14(1):80-88.
10. Gomersall SR, Skinner TL, Winkler E, Healy GN, Eakin E, Fjeldsoe B.. Feasibility, acceptability and efficacy of a text message-enhanced clinical exercise rehabilitation intervention for increasing 'whole-of-day' activity in people living with and beyond cancer. *BMC Public Health* 2019;19(Suppl 2):542.
11. Pinto BM, Dunsiger SI, Kindred MM, Mitchell S. Peer mentoring for physical activity adoption and maintenance among breast cancer survivors: moderators of physical activity outcomes. *J Cancer Surviv* 2023;17(4):1222-1220
12. Lally P, van Jaarsveld CHM, Potts HWW, Wardle J. How are habits formed: Modelling habit formation in the real world. *Eur J Soc Psychol* 2010;40(6):998-1009.
13. Weemaes ATR, Weijenberg MP, Lenssen AF, Beelen M. . Exercise training as part of multidisciplinary rehabilitation in cancer survivors: an observational study on changes in physical performance and patient-reported outcomes. *Support Care Cancer* 2022;30(11):9255-9266.
14. Howlett N, Schulz J, Trivedi D, Troop N, Chater A.. A prospective study exploring the construct and predictive validity of the COM-B model for physical activity. *J Health Psychol* 2019;24(10):1378-1391.
15. Annegarn J, Spruit MA, Uszko-Lencer NH, Vanbelle S, Savelberg HH, Schols AM et al. Objective physical activity assessment in patients with chronic organ failure: a validation study of a new single-unit activity monitor. *Arch Phys Med Rehabil* 2011; 92(11):1852-1857 e1.
16. van der Weegen S, Essers H, Spreeuwenberg M, Verwey R, Tange H, de Witte L, Meijer K. Concurrent validity of the MOX activity monitor compared to the ActiGraph GT3X. *Telemed JE Health* 2015;21(4):259-266.

17. Berendsen BA, Hendriks MR, Meijer K, Plasqui G, Schaper NC, Savelberg HH. Which activity monitor to use? Validity, reproducibility and user friendliness of three activity monitors. *BMC Public Health* 2014;14:749.
18. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Medicine & Science in Sports & Exercise* 2011;43(8):1575-1581.
19. Keteyian SJ, Brawner CA, Ehrman JK, Ivanhoe R, Boehmer JP, Abraham WT. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise parameters: implications for clinical trials and clinical practice. *Chest* 2010;138(4): 950-955.
20. Steins Bisschop CN, Velthuis MJ, Wittink H, Kuiper K, Takken T, van der Meulen WJ et al. Cardiopulmonary exercise testing in cancer rehabilitation: a systematic review. *Sports Med* 2012;42(5):367-379.
21. van der Steeg GE, Takken T. Reference values for maximum oxygen uptake relative to body mass in Dutch/Flemish subjects aged 6-65 years: the LowLands Fitness Registry. *Eur J Appl Physiol* 2021;121(4):1189-1196.
22. Brzycki M. Strength testing—predicting a one-rep max from reps-to-fatigue. *Journal of Physical Education, Recreation & Dance* 1993;64(1):88-90.
23. Levinger I, Goodman C, Hare DL, Jerums,. The reliability of the 1RM strength test for untrained middle-aged individuals. *J Sci Med Sport* 2009;12(2):310-316.
24. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *Journal of the National Cancer Institute*, 1993;85(5):365-376.
25. Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. *EORTC Quality of Life Group. Eur J Cancer* 2000;36(14):1796-1807.
26. Hinz A, Einenkel J, Briest S, Stolzenburg JU, Papsdorf K, Singer S. Is it useful to calculate sum scores of the quality of life questionnaire EORTC QLQ-C30? *Eur J Cancer Care (Engl)* 2012;21(5):677-683.
27. Hinz A, Weis J, Brahler E, Harter M, Geue K, Ernst J. Fatigue in cancer patients: comparison with the general population and prognostic factors. *Support Care Cancer* 2020;28(9):4517-4526.
28. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39(3):315-325.
29. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52(2):69-77.
30. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011;378(9798):1244-1253.
31. O'Neill L, et al. Rehabilitation strategies following esophageal cancer (the ReStOre trial): a feasibility study. *Diseases of the Esophagus* 2017;30(5):1.
32. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med* 2012;31(4):328-340.
33. van Roekel EH, Winkler EA, Bours MJ, Lynch BM, Willems PJ, Meijer K et al. Associations of sedentary time and patterns of sedentary time accumulation with health-related quality of life in colorectal cancer survivors. *Prev Med Rep* 2016;4:262-269.
34. O'Neill LM, Guinan E, Doyle S, Connolly D, O'Sullivan J, Bennett A et al. The RESTORE Randomized Controlled Trial: Impact of a Multidisciplinary Rehabilitative Program on Cardiorespiratory Fitness in Esophagogastric cancer Survivorship. *Ann Surg* 2018;268(5):747-755.

35. Sweegers MG, Boyle T, Vallance JK, Chinapaw MJ, Brug J, Aaronson NK et al. Which cancer survivors are at risk for a physically inactive and sedentary lifestyle? Results from pooled accelerometer data of 1447 cancer survivors. *Int J Behav Nutr Phys Act* 2019;16(1):66.
36. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon Get al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020;54(24):1451-1462.
37. Smith L, Lee JA, Mun J, Pakpahan R, Imm KR, Izadi S et al. Levels and patterns of self-reported and objectively-measured free-living physical activity among prostate cancer survivors: A prospective cohort study. *Cancer* 2019;125(5):798-806.
38. Roberts AL, Fisher A, Smith L, Heinrich M, Potts HWW. Digital health behaviour change interventions targeting physical activity and diet in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2017;11(6):704-719.
39. Ross R, Blair SN, Arena R, Church TS, Després Franklin BA et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* 2016;134(24):e653-e699.
40. Han M, Qie R, Shi X, Yang Y, Lu J, Hu Fet al. Cardiorespiratory fitness and mortality from all causes, cardiovascular disease and cancer: dose-response meta-analysis of cohort studies. *Br J Sports Med* 2022;56(13):733-739.
41. Dennett AM, Sarkies M, Shields N, Peiris CL, Williams C, Taylor NF. Multidisciplinary, exercise-based oncology rehabilitation programs improve patient outcomes but their effects on healthcare service-level outcomes remain uncertain: a systematic review. *J Physiother* 2021;67(1):12-26.
42. Harris TJ, Victor CR, Carey IM, Adams R, Cook DG Less healthy, but more active: opposing selection biases when recruiting older people to a physical activity study through primary care. *BMC Public Health* 2008;8:182.
43. Baumann S, Gross S, Voigt L, Ullrich A, Weymar F, Schwaneberg T et al. Pitfalls in accelerometer-based measurement of physical activity: The presence of reactivity in an adult population. *Scand J Med Sci Sports* 2018;28(3):1056-1063.
44. Weemaes ATR, Sieben JM, Beelen M, Mulder LTMA, Lenssen AF. Determinants of physical activity maintenance and the acceptability of a remote coaching intervention following supervised exercise oncology rehabilitation: a qualitative study. *Journal of Cancer Survivorship* 2023;1-13.

Appendix 3.1

Intake questionnaire remote coaching intervention according to the COM-B model

Physical capacity	I spend at least 30 minutes daily performing physical activities that make my heartrate and breathing frequency raise. (e.g. brisk walking, cycling, swimming, running fitness, ball games).	YES 52%
		NO 48%
Psychological capacity	I know what the recommended level of physical activity is according to current guideline.	YES 95%
		NO 5%
	I know what kinds of physical activities are suitable for improving my health.	YES 31%
		NO 69%
	I know what kinds of physical activities are not suitable for improving my health (e.g. because of injuries or health issues).	YES 93%
		NO 7%
	I talk regularly (at least once a week) about the theme physical activity with others.	YES 75%
Reflective motivation		NO 25%
	I know how to make a good planning, in order to perform sufficient physical activity.	YES 43%
		NO 57%
	I know how to monitor my physical activity.	YES 75%
		NO 25%
	I know how to avoid skipping planned physical activities.	YES 89%
		NO 11%
Reflective motivation	I would identify myself as someone who finds it important to be sufficiently active.	YES 75%
		NO 25%
	I am responsible for performing sufficient physical activity.	YES 100%
		NO 0%
	I am confident that I will manage to perform sufficient physical activity.	YES 100%
		NO 0%
Reflective motivation	I believe that having an active lifestyle is good for my health.	YES 86%
		NO 14%
	I believe that having an active lifestyle has a positive effects on my working- and private environment.	YES 93%
		NO 7%
Reflective motivation	I believe that performing sufficient physical activity makes people feel good.	YES 100%
		NO 0%

	I believe that performing insufficient physical activity makes people feel guilty.	YES 100% NO 0%
	I have decided to start performing sufficient physical activity.	YES 80% NO 20%
	It takes little effort for me to perform sufficient physical activity.	YES 50% NO 50%
	I am willing to give up other activities, in order to perform sufficient physical activity.	YES 77% NO 23%
	I have clearly in mind what I want to achieve during the remote coaching intervention.	YES 91% NO 9%
Automatic motivation	I encourage myself to make performing sufficient physical activity a habit.	YES 89% NO 11%
	Performing sufficient physical activity makes me feel good.	YES 95% NO 5%
Physical opportunity	I feel like I have the resources in my environment (e.g., time, money, transportation, materials needed) to perform sufficient physical activity.	YES 80% NO 20%
	I avoid situations or stimuli in my environment that prevent me from performing sufficient physical activity.	YES 43% NO 57%
	There are cues or reminders in my environment that remind me to perform sufficient physical activity.	YES 64% NO 36%
Social opportunity	I believe that most of the people I hang out with perform sufficient physical activity.	YES 64% NO 36%
	I believe that most of the people I hang out with believe I should perform enough physical activity.	YES 73% NO 27%
	I feel like I have enough social support to be perform sufficient physical activity.	YES 84% NO 16%



CHAPTER 4

Determinants of physical activity maintenance and the acceptability of a remote coaching intervention following supervised exercise oncology rehabilitation: a qualitative study

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Abstract

Purpose

The purpose of the study was to investigate perceived determinants of physical activity (PA) maintenance following supervised exercise oncology rehabilitation and the acceptability of a remote coaching intervention during this period.

Methods

A phenomenological qualitative study with semi-structured interviews was conducted. Nineteen participants (16 women, 3 men) were recruited from the intervention (n=12) and control group (n=7) of a randomised controlled trial on the effectiveness of remote coaching following supervised exercise oncology rehabilitation. Participants in the intervention group received a 6-month remote coaching intervention after completing the exercise program, aimed at stimulating PA maintenance. The interviews were based on the Capability, Opportunity, and Motivation model of Behaviour (COM-B model) and the framework of acceptability (TFA) and were coded using template analysis.

Results

Key themes regarding determinants of PA maintenance were self-efficacy, PA habits, accountability, physical complaints, and facilities. Remote coaching was perceived acceptable because it stimulated PA maintenance by offering a source of structure and social support and thereby increased accountability. Moreover, it improved confidence to perform PA, leading to increased levels of self-efficacy. The remote nature of the intervention was perceived as convenient by some of the participants, while others would have preferred additional physical appointments.

Conclusions

Cancer survivors considered remote coaching acceptable to stimulate PA maintenance following supervised rehabilitation. Interventions should focus on increasing accountability, and self-efficacy, forming habits, and helping cancer survivors to overcome barriers.

Implications for cancer survivors

The ability to maintain PA beyond supervised exercise oncology programs depends on many determinants. Remote coaching interventions have potential to target individually relevant determinants following exercise programs in cancer survivors.

Introduction

Cancer survivors can experience longstanding side effects like fatigue, declined aerobic capacity and muscle strength, psychological distress, and a diminished health-related quality of life (HRQoL).¹⁻⁵ It has been well-established that regular physical activity (PA) improves aerobic capacity and muscle strength, reduces cancer-related fatigue and psychological distress, and consequently improves HRQoL.^{6,7} A dose-response relationship exists between post-diagnosis PA and all-cause and cancer-related mortality, with risk reductions of up to 35%.⁸ Therefore, it is worrying that cancer survivors spend only 34% of their waking time in physical activity and are sedentary for the remaining time.⁹

Participation in a supervised exercise-based oncology rehabilitation program is a structured way to sustain or increase PA levels. However, existing literature suggests that cancer survivors experience difficulties with maintaining PA beyond the completion of a supervised exercise program.^{10,11} To sustain or increase the health benefits achieved during an exercise program, patients have to stay physically active. In a review about PA maintenance following exercise interventions, successful PA maintenance at 3 to 12 months was achieved in less than half of the included trials.¹² Schmidt et al. described in their qualitative study that cancer survivors experience the transition from a supervised hospital-based exercise program to independent community-based exercise as “a confrontation with the real world”.¹³

A potential way to improve the transition phase following supervised exercise programs is by supporting it with a remote coaching intervention. Remote interventions have gained popularity and are promising in the delivery of lifestyle interventions in cancer survivors.¹⁴ Two recent studies showed that remote interventions, like text messages and health coaching, delivered during and after a structured exercise program, are feasible and lead to increased PA levels in cancer survivors.^{15,16} Contrarily, Groen et al. reported in their meta-analysis that the effects of distance-based PA interventions in cancer survivors are small. However, no firm conclusions could be drawn from these findings, as the included trials had major limitations.¹⁷

In order to improve PA maintenance following supervised exercise programs in cancer survivors, it is necessary to get insight into factors that influence PA behaviour during this transition period. Ferri et al. performed a qualitative study on PA maintenance three months after supervised rehabilitation in a tertiary hospital in Australia and reported that perceived exercise benefits motivate cancer survivors to stay active after a supervised exercise program. At the same time, the transition from a supervised environment to everyday life was a significant barrier to keep exercising.¹¹ When developing or refining PA maintenance interventions, it is essential to understand PA behaviour following supervised exercise programs and the context in which this behaviour occurs. Theories of behaviour change can be used to understand and unravel the underlying mechanisms.¹⁸ The Capability, Opportunity, and Motivation model of Behaviour (COM-B model) conceptualises behaviour as part of a system of interacting factors.^{19,20} In the current study, perceived determinants of PA maintenance will be explored from the perspectives of the COM-B model.

Even when effective, implementation of interventions that support PA maintenance is only likely to succeed when these are acceptable for the target population. The Theoretical Framework of Acceptability (TFA), defines acceptability as 'a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate. The TFA comprises seven domains (i.e. affective attitude, self-efficacy, perceived effectiveness, ethicality, intervention coherence, burden, and opportunity costs).²¹ The TFA is considered to be helpful in assessing the acceptability of complex healthcare interventions within the development, piloting and feasibility, outcome and process evaluation, and implementation phases, as described by the Medical Research Council (MRC) guidelines.^{21,22}

Dennett et al. reported that an 8-week tele-rehabilitation program was perceived acceptable in cancer survivors.²³ Results from Gell et al. indicate that a remote coaching intervention is acceptable to improve PA maintenance following a supervised exercise program.²⁴ To our knowledge, no studies have been performed yet on the acceptability of remote coaching following supervised oncology rehabilitation, using the TFA model.

The first aim of this study was to get insight into perceived determinants of PA maintenance in the transition from a supervised exercise oncology rehabilitation program to habitual PA in the community. The second aim was to assess the acceptability of a 6-month remote coaching intervention to stimulate PA maintenance following a supervised exercise program in cancer survivors.

Methods

Study design and theoretical frameworks

A qualitative study design with a phenomenological approach was used and semi-structured interviews were conducted. Procedures of data collection complied with the Declaration of Helsinki and were approved by the Ethical Review Board of Maastricht University Medical Centre (MUMC+) (registration number 18-050). Results were reported according to the Consolidated criteria for Reporting Qualitative research (COREQ).

The interviews investigated:

- (1) the perceived determinants of PA maintenance following a supervised oncology exercise program. This part was explorative in nature, using the COM-B model as a theoretical framework. An explorative approach was applied to entangle the complex interaction of factors influencing PA behaviour;
- (2) the acceptability of a remote coaching intervention in this period. This part was explanatory in nature, using the framework of acceptability (TFA) as a theoretical basis.

COM-B Model

PA maintenance was explored from the perspective of the COM-B model. In this model Capability (physical and psychological), Opportunity (social and physical), and Motivation (reflective and automatic) are seen as drivers of Behaviour. Motivation is the central mediator of the model which is affected by Capability and Opportunity (Figure 4.1). In the COM-B model, behaviour is seen as part of a complex system of interacting factors.^{19,20} The interpretation of the constructs of the COM-B model in the current study is described in Appendix 4.1. The analysis of perceived determinants of PA maintenance had an explorative approach because the contribution of the

different constructs of the COM-B model to PA maintenance is complex and remains unknown. Focusing only on these distinct constructs might result in a thin description of determinants without getting to the root of the problem of PA maintenance.

Therefore, the COM-B constructs were guiding during the interviews and analyses but not restrictively defining, and key themes were allowed to emerge apart from the constructs of the model.

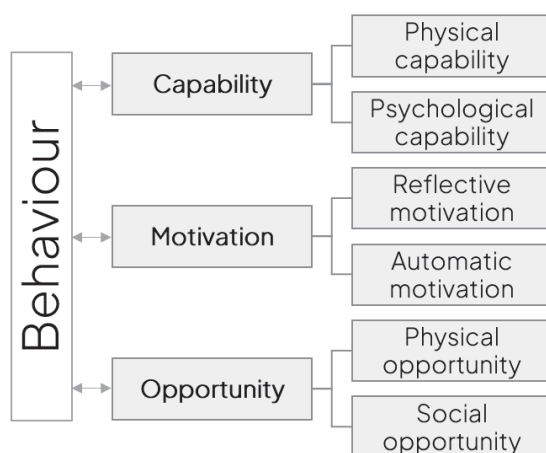


Figure 4.1. COM-B Model. Reproduced from Michie et al.¹⁹ COM-B Model = Capability, Opportunity, and Motivation model of Behaviour.

TFA

The analysis of intervention acceptability was based on the constructs of the TFA (i.e. affective attitude, self-efficacy, perceived effectiveness, ethicality, intervention coherence, burden, opportunity costs). The interpretation of these constructs as applied to our context is described in Appendix 4.1. In the TFA model, all aspects of acceptability are captured in the different constructs.²¹ These constructs were used explanatory, meaning that the interviews aimed to gain insight into whether, to what extent, and how each construct contributed to the overall acceptability of the intervention. An explanatory approach was chosen because each of the constructs of the TFA explains an essential part of the acceptability and therefore should be included, but additional overarching themes were allowed to emerge as well.

Study context

Participants for this study were recruited from a randomised controlled trial (RCT) on the effectiveness of 6-month remote coaching following a 10-week supervised exercise program as part of multidisciplinary oncology rehabilitation at the MUMC+, Maastricht, The Netherlands. The MUMC+ is a university hospital and is recognised as a Comprehensive Cancer Centre by the Organisation of European Cancer Institutes. The supervised exercise program was part of usual care and the content of this program is described elsewhere.²⁵ After completion of the supervised program, 97 participants were included in the RCT and randomised to either the intervention group or the control group. The control group (C) received no additional interventions after completing the supervised exercise program. Participants in the intervention group (I) received a remote coaching intervention. Measurements of PA behaviour and physical- and psychosocial functioning were carried out at baseline and after six months.

The remote coaching intervention

The 6-month remote coaching intervention was delivered by a community-based sports organisation (Maastricht Sport, Municipality of Maastricht, The Netherlands) and aimed to stimulate patients to increase their PA levels. This intervention was not newly developed but was identified as potentially beneficial for PA maintenance in cancer survivors following a supervised exercise program and is now tested in the evaluation phase of the MRC framework, in the current study and the RCT. Involved coaches had at least a bachelor's degree in Sports Science or Sports and Movement Education, were trained in behaviour change techniques, and had experience with delivering the intervention. During a face-to-face intake assessment at the Department of Physical Therapy at the MUMC+, the coach obtained information about the subjects' personal motivation and PA preferences using the COM-B model. The coaches identified facilitators and barriers for behaviour change in these three constructs and adapted the coaching accordingly. After the intake, the program consisted of individually tailored, remote coaching. The coaching took place via phone calls or e-mails, depending on personal preferences. In the first three months, the coach approached the subjects weekly. Thereafter, the coach evaluated the individual progress, and the frequency was reduced to one contact moment per month.

Participants

Criterion sampling was used to recruit participants from both the intervention group (I) and the control group (C) of the RCT until data saturation²⁶ was reached. The eligibility criteria for this study were the same as for the RCT. Patients were eligible to participate in this study when they were ≥ 18 years of age; were suffering from physical, and/or psychosocial complaints and/or chronic fatigue; had completed active medical treatment (i.e. surgery, chemotherapy, radiotherapy, stem cell transplantation) and a 10-week exercise program, as part of multidisciplinary oncology rehabilitation. Patients were excluded if they had insufficient understanding of the Dutch language, were in an unstable phase of disease (e.g. receiving palliative treatment), scheduled for chemotherapy, radiation, or invasive surgery in the six months after completing the exercise program, and if they were unable to perform exercise activities without supervision (i.e. because of risk of falling or injuring). They were approached to participate during a phone call for planning their follow-up measurement for the RCT. All participants gave written informed consent.

Interview procedures

Face-to-face, semi-structured interviews took place at the Department of Physical Therapy at MUMC+. Interviews were planned on the same day as the follow-up measurements for the RCT and took approximately 30 minutes. To avoid bias, interviews were conducted by an independent researcher (NS) not involved in the rehabilitation program or the RCT. A second independent researcher (LM) was present to take field notes, check for interview completeness, ask additional questions when needed, and give a verbal summary for verification at the end. Participants received a written summary of the interview for a member check. The interview guide was designed by the researchers a priori, based on the COM-B model (exploratory) and TFA (explanatory), and was adapted once, after the seventh interview, to add more in-depth questions to further explore the initial interview guide's themes (Appendix 4.2). Interviews were recorded using a digital voice recorder and transcribed verbatim afterwards. Recordings were deleted after transcription was completed.

Coding and analysis

Template analysis²⁷ was conducted to code the transcripts, using NVivo V.12. Coding was performed by two researchers (NS, AW) who were guided by a third, experienced qualitative researcher (JS). An a priori coding template was developed, based on the COM-B model and the TFA. Subsequent template versions evolved and were allowed to deviate from the initial frameworks, based on emerging topics. After coding the first interview, the template was adapted to an initial template. After each two to three interviews the coding template was adapted based on emerging topics. Codes were added, removed, or merged as appropriate. The transcripts of the first three interviews were coded independently by two researchers and discussed afterwards until consensus was reached. After the first three interviews, transcripts were coded by one researcher and discussed afterwards with a second researcher for researcher triangulation. After 16 interviews, the fifth and final version of the coding template was formed. During the last three interviews, no new codes emerged for both research aims, which indicated that code saturation was reached.²⁶

Researcher characteristics and reflexivity

In this paragraph, the background and characteristics of researchers involved in data collection and analysis are reported, in order to provide insight into possible researcher biases. During the course of the study, AW was working at the Department of Physical Therapy of the MUMC+ as an embedded scientist in the field of human movement science. She was working partly as a physical therapist, specialised in exercise oncology rehabilitation and treating patients with neurological disorders. At the same time, she was working as a PhD candidate in the field of oncology rehabilitation. The current study and the aforementioned related RCT were part of her PhD project. Because of her close involvement in this research and the patients in the oncology rehabilitation, she did not conduct the interviews and worked together with independent researchers (NS, LM, and JS) during data analysis in order to minimize the risk of bias. NS got her Bachelor's degree in physical therapy, was an MSc Human Movement Science student at the time of the study, and was working as a research trainee at the Department of Physical Therapy of the MUMC+. LM was employed as a physical therapist specialised in orthopaedics and geriatrics and PhD candidate in the field of orthopaedics, at the Department of

Physical Therapy of the MUMC+. JS was working as an associate professor at the Department of Anatomy and Embryology at the University of Maastricht and is a senior researcher in the field of human movement science, with experience in qualitative research and a focus on physical therapy. TL was working as a professor of Hospital-based Physical Therapy and has contributed to several qualitative studies in this field. MB was working as a sports physician and senior researcher in the field of oncology. They have both provided supervision during the course of the study and their expertise contributed to triangulation. AW, NS, LM, and MB had less experience with qualitative research but they received the necessary training and worked closely together with JS and TL during the conduct of this study.

Results

Participants

Between March and June 2021, twenty-two patients were eligible to participate in this study. Three of them declined because of the required time investment or personal reasons, resulting in a final sample of 19 participants (16 women / 3 men). All participants answered questions about determinants for PA maintenance. Twelve participants (63.2%) received the coaching intervention and answered questions about the acceptability of this intervention, additionally. The participant characteristics and group distribution are described in Table 4.1.

Results part I: Determinants for PA maintenance

Key themes regarding perceived determinants of PA maintenance were self-efficacy, PA habits, accountability, physical complaints, and facilities. These themes are explained below with quotes and related determinants. In addition, key themes and perceived determinants were clustered according to the constructs of the COM-B model in Figure 4.2.

Table 4.1. Participant characteristics.

Participant	Group (I/C)	Sex (F/M)	Age category (years)	Cancer diagnosis	Medical treatment	Time since treatment completion * (months)
P01	I	F	46-55	Breast	Surgery; CT	13-15
P02	I	M	56-65	Colorectal	Surgery	16-18
P03	C	F	46-55	Breast	Surgery; RT	13-15
P04	I	F	56-65	Breast	Surgery; CT; RT; HT	13-15
P05	C	F	18-35	Breast	Surgery; CT; RT; IT	16-18
P06	I	F	56-65	Breast	Surgery; RT	16-18
P07	I	F	56-65	Breast	Surgery; CT; RT; HT	13-15
P08	C	F	18-35	Breast	Surgery; CT; RT	9-12
P09	I	F	56-65	Breast	Surgery; CT; HT	9-12
P10	C	F	>65	Lung	CT; RT	13-15
P11	C	F	56-65	Oesophagus	Surgery; CT; RT	13-15
P12	I	M	56-65	Prostate	Surgery; RT	13-15
P13	I	M	35-46	Testis	Surgery; CT	9-12
P14	I	F	18-35	Leukaemia	CT	13-15
P15	I	F	>65	Breast	Surgery; CT; RT; IT; HT	13-15
P16	C	F	56-65	Breast	Surgery; CT; RT	9-12
P17	I	F	36-45	Melanoma	Surgery	13-15
P18	I	F	>65	Lymphoma	CT; IT	9-12
P19	C	F	36-45	Breast	Surgery	16-18

*Time since active medical treatment, hormone therapy, and immunotherapy not included
 I=Intervention Group of the RCT; C=Control Group of the RCT; F=Female; M=Male;
 CT=Chemotherapy, RT= Radiotherapy, HT=Hormone Therapy, IT=Immunotherapy.

Self-efficacy

Participants described that confidence to perform PA enabled them to maintain PA levels and overcome perceived barriers. In contrast, feelings of insecurity and incompetence discouraged patients from being active, even when the circumstances were optimal. This kind of behavioural control is often referred to as 'self-efficacy' and this topic came up frequently during the interviews. Self-efficacy is seen as an important part of reflective motivation and can be defined as "people's belief in their capabilities to take control over their own functioning and over events that affect their lives".²⁸ Level of self-efficacy seemed to be related to many other perceived determinants and was therefore an important key theme. Some participants mentioned that they experienced PA as a way to take control of their recovery.

P08(C): "Exercising gives me the feeling that I have influence over my recovery. It's hard for me to let go of control, and this puts you in control."

Some participants had intentions to perform PA regularly but did not believe they were capable of sustaining it. In these cases, the inability to maintain PA levels seemed to be related to a lack of self-efficacy.

P01(I): "When you are walking on the treadmill in the hospital you know you have to, so you just do it. Someone is standing next to you and you just keep going, because you know you have to and you feel safe with that person. But at home, you ask yourself 'Why do I have to do that?' I am too weak and something might happen or I might fall."

Self-efficacy was increased by positive beliefs about and experiences with PA. Reflections about potential benefits were enablers for PA maintenance because participants wanted to take control over their own functioning. The belief that PA could improve recovery and general health and reduce the risk of cancer recurrence increased the level of self-efficacy regarding PA maintenance. Participants also believed and experienced that PA leads to improved energy levels and physical and mental state.

P01(I): "I don't want the cancer to come back. I don't think it will, but I noticed that I feel better after walking or exercising. When you stay physically active, you get healthier, you can breathe better. And also mentally... It's something you can do for yourself, for your health."

For some participants, their cancer diagnosis was a 'wake-up call'. It increased their awareness about the benefits of healthy living and the role of PA in this, leading to higher levels of self-efficacy.

P13(I): "It was a wake-up call, my disease. I wanted to take care of myself and wanted to get back on my feet. Well, yes that was actually my biggest motivation to exercise."

Reaching high levels of self-efficacy for PA maintenance is not only the result of reflective motivation but also requires certain psychological capabilities. This includes understanding the risks of an unhealthy lifestyle, but also capabilities for planning and decision-making. Participants reported that attention and time for PA in daily-life time schedules, but also

decisions about priorities in life often changed after the diagnosis of cancer.

P14(I): "Physical activity is important and it's higher on my priority list now. If it's necessary I just reschedule work or other things."

When PA was not considered a priority, this was mostly not literally mentioned during the interviews. However, one participant mentioned that getting fit was not 'top of mind' at that moment, because of changes in daily routines and the preference to take it slow during recovery. Perceived determinants related to the self-efficacy theme could be linked to the following constructs of the COM-B model: *reflective motivation* and *psychological capability* (Figure 4.2).

PA habits

During the interviews, participants who successfully maintained PA often shared their experiences with the process of habit-forming. When participants regularly performed PA before their diagnosis, this positively affected PA maintenance because they already had a PA routine before and could pick up their old schedule. These participants with prior PA habits often expressed positive emotions towards PA. Besides, participants who already performed PA in the past seemed to be more confident about their capabilities for PA maintenance, leading to higher levels of self-efficacy.

P08(C): "For me it was not that hard to sustain it, to stay physically active, because I have always been before. Before the diagnosis as well. I just really enjoy hiking."

Some participants were able to form PA habits during the study period, while they did not perform regular PA before.

P13(I): "I came to the point that my PA behaviour was stable, as a part of my routine. I used to exercise before occasionally. Now it's more structured and I'm able to sustain it."

Habits are the result of automatic brain processes and determinants related to habits belong to the construct of *automatic motivation* in the COM-B model (Figure 4.2).

Accountability

Participants mentioned that they needed some kind of structure to make PA part of their routine. Scheduled appointments with others were seen as a source of structure and were perceived to increase accountability for PA maintenance. Accountability can be defined as “the fact of being responsible for your decisions or actions and being expected to explain them when you are asked”.²⁹ Accountability was a key theme during the interviews and was discussed from several perspectives.

Participants reported that they felt accountable for showing up when they had an appointment with their physical therapist, sports instructor, or peers. For some participants who received coaching, the expectation of the next phone consultations made them feel accountable for PA maintenance. When a phone consultation was scheduled with the coach, they knew they would be asked to report on their PA behaviour and they felt accountable to perform PA. In this way, accountability did also increase the level of self-efficacy, because the fact that participants had an appointment they had to meet, or an expectation to fulfil, made them feel more confident about being able to stick to their PA plans.

P04 (I): “I liked that I received a phone call once a week, which gave me a feeling of accountability. It is a good thing to be more or less accountable for physical activity, because you know you have to report it to the coach. It’s the same with an appointment to participate in a group-based exercise activity, which I believe you would only cancel if you have a good reason for it. Therefore, you’re more likely to participate in that activity.”

P03(C): “Unfortunately, I have little self-discipline to start exercising. I know that it’s good for me, but it just works better if someone tells me ‘You have to be there at a certain time’ or ‘Why did you not show up last week?’. I just need that kind of structure to feel accountable.”

Accountability relies on an expected social interaction and is therefore closely related to social support.³⁰ Respondents mentioned that social support motivated them for PA maintenance. Sometimes this support was offered by relatives who actually exercised together with the patients, but other forms of support were mentioned as well, like social support from the coach, peer support, playing with grandchildren, or walking the dog. Participants felt accountable to relatives who supported their PA behaviour because they wanted to fulfil their expectations.

P04(I): “The grandchildren told me ‘Grandma, you have to exercise!’ My granddaughter told me: Come on, grandma, let’s go’. That stimulated me. Or my grandson who said: ‘Grandma, you have to lift me, that will make you strong’.

Social support did not only offer structure through accountability, but it made PA also more fun and enjoyable, resulting in positive emotions towards PA.

P09(I): “With support, or a sports club or something it’s easier for me. I find it more enjoyable and fun and I’m better able to keep up with it.”

Determinants related to accountability can be linked to the construct *social opportunity* in the COM-B model. (Figure 4.2)

Physical complaints

The influence of physical complaints on PA maintenance was discussed. Even after completing the supervised exercise program, participants were often confronted with physical complaints. Chronic fatigue and treatment side effects were often mentioned during the interviews. When patients experienced these kinds of physical disabilities, this was a barrier for PA maintenance.

P01(I): “The hormone therapy was really bad for my body. The side effects almost turned me disabled. I had difficulties with standing up, with walking. Therefore, the doctor and I decided to stop the hormone therapy and that was a very positive experience! I felt much better and was able to walk and cycle!”

Some patients mentioned physical complaints but described how they maintained PA despite this. The ability to cope with physical complaints seems to depend on the level of self-efficacy. Some patients were capable of maintaining PA when experiencing physical complaints or were able to pick up PA habits after recovering, while others could not. Some participants felt like they were caught in a 'vicious circle'. They felt incapable to perform PA because of physical complaints and consequently felt less fit, more fatigued, or even depressed as a result of being inactive.

Not only the presence of but also the fear of developing physical complaints was a barrier for PA. Some participants had a fear of injury when exercising independently. The confidence to perform PA independently was related to the patient's level of efficacy.

P12(C): "If you do it all by yourself, the chance of getting injured is very high. You have to perform the right exercises."

Physical complaints can be linked to the construct of *Physical Capability* in the COM-B model (Figure 4.2).

Facilities

The accessibility of sports and rehabilitation facilities and thereby PA maintenance were negatively affected by the COVID-19 pandemic and related measures. This topic often emerged during the interviews. Some respondents reported that they managed to maintain PA levels until the COVID-19 pandemic commenced, but failed to continue when facilities had to close. The ability to adapt their PA routine in this situation differed between respondents and was related to the level of self-efficacy.

P04(I): "COVID-19 was a disadvantage, has made things hard, because going to exercise independently (in community-based facilities, which had to close) was just not possible."

The theme of facilities is related to the constructs of *physical opportunity* in the COM-B model (Figure 4.2).

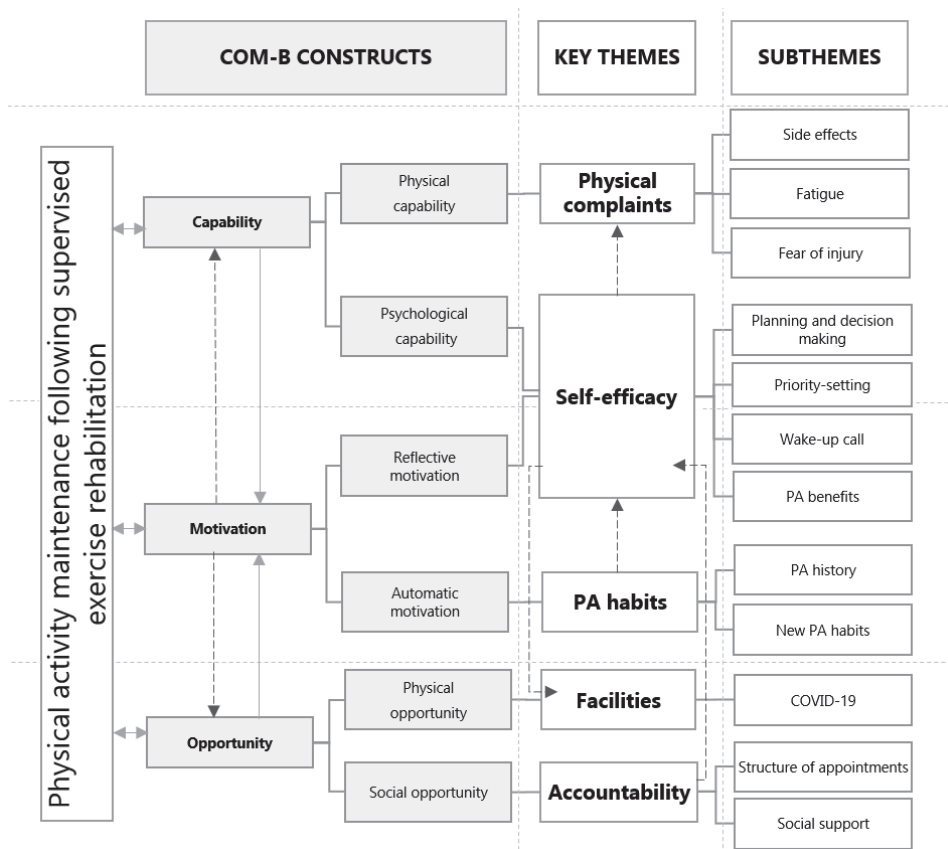


Figure 4.2. Key determinants and determinants of physical activity maintenance following supervised exercise rehabilitation, clustered in the constructs of the COM-B model. Arrows to show the relation between key themes, with self-efficacy as a central theme.

Results part II: Acceptability of the coaching intervention

The seven constructs of the TFA were discussed with participants who received the coaching intervention (n=12), to get insight into whether, to what extent, and how each of the constructs contributed to the overall acceptability of remote coaching. In addition, three TFA overarching key themes were determined. Overlap was seen with the key themes for determinants of PA maintenance in part I. The first key theme is accountability since the remote coaching intervention offered structure and social support thereby leading to an increased feeling of accountability. This influenced the affective attitude as well as the

perceived effectiveness of participants towards the intervention. The level of self-efficacy was the second key theme for the acceptability because respondents' belief in their capabilities to follow the advice of the coaching determined the perceived effectiveness. Besides, participants mentioned that the coaching made them feel confident, which could lead to an increase in the level of self-efficacy. The third overarching theme was the remote nature of the intervention, which was convenient for some participants, but not for others. The participants' experience with the remote nature of the intervention influenced their affective attitude, perceived effectiveness, self-efficacy, and the burden.

Affective attitude

Overall, participants had positive experiences with the coaching intervention. They appreciated the personal contact, attention, and kindness of the coaches.

P18: "It is about the attention. She was asking me how it went and I told her what PA activities I did that week and that was nice."

Participants also described that the remote coaching intervention made them feel accountable for performing PA.

P02: "It is nice to have an appointment that makes you feel accountable to perform physical activity like you intended. To report how it went and to be more or less accountable."

However, some participants would have preferred a coaching intervention with physical appointments. They felt a phone call was not enough to motivate them. It should be noted that for some of the participants, even the first appointment, which is usually a physical appointment, had been via a phone call, due to COVID-19 restrictions.

P12: "If they really have to stimulate me to perform PA, because I can't do it, or because I'm not motivated, then a phone call is not enough. Then you really need to see someone face-to-face."

Self-efficacy

As already described in the first part of this article, self-efficacy is a key theme in PA maintenance. In the TFA, self-efficacy refers to persons' confidence about their ability to perform the required behaviour. Most participants described that they felt confident to follow the coaches' advice. They mentioned that PA advices were personalised and based on shared decision-making. However, for some participants it was difficult to stay active, despite the advice from the coach, indicating low levels of self-efficacy.

P04: "I feel bad about myself, that I'm not capable to do it all by myself. I just can't do it. She called me and asked 'is there anything I can do for you?' But in the end, I have to do it by myself, right?"

Perceived effectiveness

The majority of participants believed the coaching intervention was effective for improving PA maintenance. They mentioned that the coaching stimulated them to maintain PA, by offering a source of structure, accountability, social support, and confidence after the supervised exercise program.

P07: "Without the motivational coaching intervention I would not have exercised, I am 100% sure about that. Maybe I would have performed an online program for three or four weeks, but then I would have stopped. The coaching really offered me a structure to keep exercising."

However, a few participants perceived no effect, because they had the feeling they had to perform PA by themselves and the advice did not help them with this, or because they already felt capable to perform PA independently without coaching.

P12: "I believe the coaching is effective for people who need it, but for me it was just a pleasant short chat. I could not say that it helped me."

Ethicality

Expectations about the coaching intervention were diverse. Some of the participants well-understood the content of the intervention beforehand because they read about it in the research participant information. Others did not know what to expect or expected exercise training given by a sports coach instead of remote coaching.

P13: “Actually I didn’t know exactly what it would entail, the coaching. But they already told me that it was not someone who sets up a training program for you, it’s more like a source of accountability, someone who contacts you.”

Participants mentioned that the added value of the coaching intervention might differ between individuals, depending on their personal needs. They believed that especially persons who have difficulties with maintaining PA, might benefit from the coaching.

P17: “For people who have difficulties with exercising, or who don’t regularly perform exercise, I think it might increase accountability and give extra motivation to push through. I think it depends on the person.”

Intervention coherence

Participants well-understood the aim of the coaching intervention and were able to describe this. Stimulating PA maintenance and motivation were most often mentioned as the main goal. Participants also related the aim of this intervention to health improvement, showing they were aware of PA benefits.

P17: “To motivate people for physical activity and to sustain it. And to actually become aware of the importance. We all know that physical activity is important and healthy, but you have to keep doing it.”

While the goal of the intervention was clear, some participants questioned whether remote coaching was the most appropriate mode of delivery. They believed that physical appointments were needed to stimulate PA maintenance.

Burden

The majority of participants did not experience the coaching intervention as a burden. They thought it was convenient to receive the coaching by phone and mentioned that the planning by the coaches was flexible. Two participants experienced the calls as a burden sometimes, when the coaches called while they were busy.

P13: "It was no burden because the coach was very flexible. We had an appointment at a certain time, but when that turned out to be inconvenient she called half an hour later."

The remote nature of the intervention positively affected the acceptability of the intervention in some participants and negatively affected it for others.

Opportunity costs

No opportunity costs were mentioned during the interviews.

Discussion

The aim of this qualitative study was twofold. First, we wanted to explore determinants of PA maintenance during the transition from supervised exercise oncology rehabilitation to habitual PA in the community. Second, we wanted to investigate whether and for what reasons a remote coaching intervention was perceived acceptable by cancer survivors during this period.

Determinants for PA maintenance were explored and five key themes were identified, covering and linking all constructs of the COM-B model. The Capability of participants to maintain PA was dependent on physical complaints (physical capability) and on the level of self-efficacy needed for tasks like planning and priority-setting (psychological capability). Self-efficacy was not only dependent on patients' capability but also related to their motivation for optimising health and recovery (reflective motivation). Besides, motivation for PA maintenance relies on automatic habitual processes, and patients with prior PA habits are more likely to successfully maintain PA (automatic motivation). The possibility of participants to

maintain PA was dependent on the accessibility of facilities, which was negatively affected by the COVID-19 pandemic (physical opportunity), and on their accountability for PA maintenance, which was reinforced by social support (social opportunity). The fact that physical complaints like chronic fatigue and treatment side effects emerged as a perceived barrier for physical activity after supervised rehabilitation following medical treatment, implies that more support is needed to achieve long-term PA. Reassurance and encouragement by healthcare providers, including the physician, are required for patients to be able to overcome these barriers. Patients should be informed that performing PA is safe for them and even beneficial. Moreover, the fact that cancer survivors still experience side effects long after completion of the treatment, advocates the integration of survivorship care earlier in the patient journey to prevent for side effects.

According to the COM-B model, Motivation is the central mediator of behaviour, which is affected by Capability and Opportunity. However, we believe that Motivation conversely affected the Capability and Opportunity to maintain PA as well. Patients with higher levels of self-efficacy were more likely to overcome barriers in the construct of Capability and Opportunity, like the burden of and fear of physical complaints and the limited accessibility of facilities during the COVID-19 pandemic. Patients who had high levels of self-efficacy believed in their capabilities to perform PA despite these barriers and were able to overcome them, while patients who did not, mentioned that they could not perform PA because of these barriers. Therefore, arrows were added in Figure 4.2, pointing back from Motivation to Capability and Opportunity. These findings confirm the statement of the COM-B model that behaviour is a complex process which is partly an entangled system of interacting factors.^{19,20}

Remote coaching was perceived as generally acceptable to cancer survivors who completed a supervised exercise program. Key themes for acceptability were self-efficacy, accountability, and the remote nature of the intervention. Participants reported that the coaching had positive effects on PA maintenance, by offering structure and confidence, and consequently improving accountability and the level of self-efficacy. The perceived effectiveness was also dependent on the level of self-efficacy. This implies that it could be useful to assess the level of self-efficacy at the start of a remote coaching intervention and adapt the coaching

accordingly. The remote nature of the intervention positively affected the acceptability in some participants and negatively affected it in others. Some participants would have preferred face-to-face appointments instead of or in addition to phone calls, while others found the remote nature convenient

Our findings about determinants for PA maintenance were broadly in line with those of previous studies. Gell et al. explored female cancer survivors' perspectives on remote coaching interventions to improve PA maintenance and identified five themes with great similarities to our study findings: accountability to a remote partner; plan Bs planning for barriers; the habit cycle; convenience through technology; and reclaiming health ownership.²³ Ferri et al. reported that the transition from a supervised environment to everyday life was a significant barrier to maintain exercise participation following a hospital-based exercise program. Participants had concerns about fitting exercise in daily life, particularly because participants would return to work.¹¹ This concern did not emerge during the interviews of the current study, which could be explained by the fact that some participants in our study did not return to work yet in the 6 months after completing the exercise program, or were retired. Although not specifically related to work, difficulties with fitting PA into everyday life were mentioned during the current study as well. Cantwell et al. conducted an exploratory, qualitative study of the experiences of patients across the cancer journey.³¹ They reported that regular PA provided a "vehicle for recovery" and created a sense of "self-power", which is in line with our findings about self-efficacy. Environmental, patient-related, and treatment-related barriers were reported as well and were similar to our findings. In contrast to our study, financial costs were a perceived barrier for PA participation. In the current study, the financial burden was discussed in some interviews but was never a reason to quit PA participation. This may be due to the fact that options for insurance-covered, low-cost, or even free PA activities were discussed with the participants at the end of the exercise program. These findings emphasise the importance of the availability of PA-promoting interventions for all cancer survivors, regardless of their financial status. Telehealth interventions have the potential to reach many patients, requiring fewer resources than face-to-face interventions.¹⁴ The current and previous findings fit within the Cancer Rehabilitation to Recreation (CaReR) Framework. In the CaReR Framework, a stepped-care approach is

proposed, considering the importance of behaviour change and routine assessment. In accordance with our findings, the framework emphasised the importance of self-efficacy, by recognising that the most suitable settings of PA interventions vary depending on the level of self-efficacy and recognising that PA counselling should be offered throughout the patient journey to build self-efficacy.³²

Our findings about the acceptability of remote coaching had similarities with the findings of a review about the use of telehealth in cancer survivors. In this review, high satisfaction with remote interventions was reported, but the importance of customization was emphasized. The preference for in-person follow-up was reported, like in our study, and visual elements were appreciated when interventions were remote.³³ These findings indicate that a combination of physical and remote appointments could be a future solution and video calls could potentially add benefit compared to normal phone calls. Gell et al. describe that remote interventions are acceptable to support PA in female cancer survivors, when known preferences are incorporated, to focus on personal intentions and goals.²⁴ In the current study, personal preferences were mapped during the intake appointment using the COM-B model and incorporated into the remote coaching intervention. Although the coaching intervention was generally considered acceptable, participants mentioned that the added value of the intervention depended on personal needs. During this study, all participants in the intervention group of the RCT received the coaching intervention. However, in daily practice, remote coaching following a supervised exercise program should be offered only when patients need it, are open to it, and if the intervention matches or can be tuned to their personal needs and preferences. Triage would be required to determine if there is an indication for PA maintenance interventions and which intervention is most suitable. The optimal mode of delivery, content, duration, and intensity of the coaching might depend on personal factors, like the patient's social environment and their level of self-efficacy, and should be personalised. The integration of triage and stratification could be based on comparable interventions, which are already successfully implemented, like the Coach2Move approach.³⁴ This is a personalised and goal-oriented physical therapy intervention aimed at improving long-term levels of physical activity in which patients are stratified to one of three intervention profiles with a pre-defined number of sessions. The intervention is provided face-to-face

and future research should explore the potential of combining physical and remote appointments. Foster et al. identified determinants of PA maintenance in patients with gastrointestinal cancer and reported that patients will likely need minimal support for PA maintenance when they perform a PA activity they enjoy. Besides, they describe that participants who have a history of exercising, hold strong values of PA importance, which is in line with our findings about PA habits.³⁵

A strength of this study was the fact that perceived determinants for PA maintenance after a supervised exercise program were assessed in both cancer survivors who did and did not receive a follow-up intervention. In this way, we tried to get insight into patients' experiences with this transition phase from multiple perspectives. Furthermore, the acceptability of a potential intervention for PA maintenance was investigated, which is important for optimising the intervention and successful implementation in daily practice. A novel aspect of this study can be found in the contribution of telehealth to promote PA maintenance in cancer survivors. The fact that we included mainly women with breast cancer can be seen as a study limitation. Besides, all participants took part in an RCT to the effectiveness of remote coaching following supervised exercise rehabilitation. Participants who were included in this RCT were potentially more motivated for PA and their behaviour and opinions may have been influenced by the research information. Because of these reasons, the findings of this study might not be transferable to all cancer survivors. Finally, this study was conducted during the COVID-19 pandemic. Findings about determinants for PA maintenance and acceptability of remote coaching would probably have been different if not examined during the COVID-19 pandemic.

Future studies should focus on identifying cancer survivors at risk for turning inactive following structured exercise programs and designing appropriate follow-up interventions for patients with different needs. Since it could be challenging to reach and motivate these patients to participate in these interventions, appropriate methods to achieve this should be investigated as well. Besides, future research should focus on further evaluation, refinement, and implementation of the remote coaching intervention. We would propose to use the MRC framework for complex interventions to guide these future steps.²²

Conclusion

In conclusion, the findings of the current study implicate that the transition from supervised rehabilitation to daily life PA is influenced by a variety of determinants that are related to the Capability, Opportunity, and Motivation of the patient. The level of self-efficacy plays a major role in the ability to maintain PA following supervised rehabilitation. Besides, the formation of PA habits, the feeling of accountability, the presence of and fear of physical complaints, and the accessibility of facilities were reported. A remote coaching intervention to promote PA maintenance was perceived acceptable to cancer survivors who participated in a supervised exercise program but could be improved by adding face-to-face appointments. Participants experienced the remote coaching intervention as a source of structure, accountability, social support, and self-efficacy, but the perceived added value of the intervention differed between participants. We believe that interventions for PA maintenance need a personalised approach and should focus on habit-forming and improving self-efficacy, helping patients to overcome PA barriers like work schedules, treatment-related side effects, and adapting during crises like a pandemic.

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References

1. Ebede CC, Jang Y, Escalante CP. *Cancer-Related Fatigue in Cancer Survivorship*. Med Clin North Am 2017;101(6):1085-1097.
2. Jean CY, Syrjala KL. Anxiety and depression in cancer survivors. Medical Clinics 2017;101(6):1099-1113.
3. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol 2012;30(20):2530-2537.
4. Marques VA, Ferreira-Junior JB, Lemos TV, Moraes RF, Junior JRS, Alves RR et al. Effects of Chemotherapy Treatment on Muscle Strength, Quality of Life, Fatigue, and Anxiety in Women with Breast Cancer. Int J Environ Res Public Health 2020;17(19):7289.
5. Nayak MG, George A, Vidyasagar MS, Mathew S, Nayak S, Nayak BS et al. Quality of Life among Cancer Patients. Indian J Palliat Care 2017;23(4):445-450.
6. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev 2017;52:91-104.
7. Kessels E, Husson O, van der Feltz-Cornelis CM. The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis. Neuropsychiatr Dis Treat 2018;14:479-494.
8. Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis. JNCI Cancer Spectr 2020;4(1):pkz080.
9. Sweegers MG, Boyle T, Vallance JK, et al. Which cancer survivors are at risk for a physically inactive and sedentary lifestyle? Results from pooled accelerometer data of 1447 cancer survivors. Int J Behav Nutr Phys Act 2019;16(1):66.
10. Cheifetz O, Dorsay JP, MacDermid JC. Exercise facilitators and barriers following participation in a community-based exercise and education program for cancer survivors. J Exerc Rehabil 2015;11(1):20-29.
11. Ferri A, Gane EM, Smith MD, Pinkham EP, Gomersall SR, Johnston V. Experiences of people with cancer who have participated in a hospital-based exercise program: a qualitative study. Support Care Cancer 2021;29(3):1575-1583.
12. Spark LC, Reeves MM, Fjeldsoe BS, Eakin EG. Physical activity and/or dietary interventions in breast cancer survivors: a systematic review of the maintenance of outcomes. J Cancer Surviv 2013;7(1):74-82.
13. Schmidt MLK, Ostergren P, Cormie P, Ragle AM, Sonksen J, Midtgaard J. "Kicked out into the real world": prostate cancer patients' experiences with transitioning from hospital-based supervised exercise to unsupervised exercise in the community. Support Care Cancer 2019;27(1):199-208.
14. Goode AD, Lawler SP, Brakenridge CL, Reeves MM, Eakin EG. Telephone, print, and Web-based interventions for physical activity, diet, and weight control among cancer survivors: a systematic review. J Cancer Surviv 2015;9(4):660-682.
15. Gell NM, Grover KW, Savard L, Dittus K. Outcomes of a text message, Fitbit, and coaching intervention on physical activity maintenance among cancer survivors: a randomized control pilot trial. J Cancer Surviv 2020;14(1):80-88.
16. Gomersall SR, Skinner TL, Winkler E, Healy GN, Eakin E, Fjeldsoe B. Feasibility, acceptability and efficacy of a text message-enhanced clinical exercise rehabilitation intervention for increasing 'whole-of-day' activity in people living with and beyond cancer. BMC Public Health 2019;19(Suppl 2):542.
17. Groen WG, van Harten WH, Vallance JK. Systematic review and meta-analysis of distance-based physical activity interventions for cancer survivors (2013-2018): We still haven't found what we're looking for. Cancer Treat Rev. 2018;69:188-203.

18. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. *Health Psychol Rev* 2015;9(3):323–344.
19. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;6:42.
20. West R, Michie S. A brief introduction to the COM-B Model of behaviour and the PRIME Theory of motivation [v1]. Qeios 2020.
21. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res* 2017;17(1):88.
22. Skivington K, Matthews L, Simpson S A, Craig P, Baird J, Blazeby J M et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance *BMJ* 2021; 374:n2061.
23. Dennett A, Harding KE, Reimert J, Morris R, Parente P, Taylor NF. Telerehabilitation's Safety, Feasibility, and Exercise Uptake in Cancer Survivors: Process Evaluation. *JMIR Cancer* 2021;7(4):e33130.
24. Gell NM, Tursi A, Grover KW, Dittus K. Female cancer survivor perspectives on remote intervention components to support physical activity maintenance. *Support Care Cancer* 2020;28(5):2185–2194.
25. Weemaes ATR, Weijenberg MP, Lenssen AF, Beelen M. Exercise training as part of multidisciplinary rehabilitation in cancer survivors: an observational study on changes in physical performance and patient-reported outcomes. *Support Care Cancer* 2022;30(11):9255–9266.
26. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant* 2018;52(4):1893–1907.
27. King N, Symon G, Cassell C. *Qualitative methods and analysis in organizational research*. London, England: Sage; 1998.
28. Bandura A, Freeman WH, Lightsey R. *Self-efficacy: The exercise of control*. Springer; 1999.
29. Hornby AS, Cowie AP. *Oxford advanced learner's dictionary of current English*. 1977.
30. Oussedik E, Foy CG, Masicampo EJ, Kammrath LK, Anderson RE, Feldman SR. Accountability: a missing construct in models of adherence behaviour and in clinical practice. *Patient Prefer Adherence* 2017;11:1285–1294.
31. Cantwell M, Walsh D, Furlong B, Loughney L, McCaffrey N, Moyna N et al. Physical Activity Across the Cancer Journey: Experiences and Recommendations From People Living With and Beyond Cancer. *Phys Ther* 2020;100(3):575–585.
34. Dennett AM, Peiris CL, Shields N, Taylor NF. From Cancer Rehabilitation to Recreation: A Coordinated Approach to Increasing Physical Activity. *Phys Ther* 2020;100(11):2049–2059.
35. Irurita-Morales P, et al. Use of Telehealth Among Cancer Survivors: A Scoping Review. *Telemed J E Health*. 2023;29(7):956–985.
36. Ward Heij, MSc and others, Implementing a Personalised Physical Therapy Approach (Coach2Move) Is Effective in Increasing Physical Activity and Improving Functional Mobility in Older Adults: A Cluster-Randomized, Stepped Wedge Trial. *Phys Ther* 2022;102(12):pzac138.
37. Foster C, Survivorship M. A typology of physical activity maintenance in people living with and beyond cancer. 2020.

Appendix 4.1

Interpretation of theoretical frameworks

COM-B Model and interpretation. *Reproduced from.*^{1,2}

Construct	Interpretation
Capability	Psychological and physical capacity for PA maintenance.
Physical capability	Physique and skills required for PA maintenance.
Psychological capability	Capacity to engage in the necessary thought processes, comprehension and reasoning for PA maintenance.
Opportunity	All the external factors that lie outside an individual that make PA maintenance possible or prompt it.
Physical opportunity	Inanimate parts of the environmental system and time affecting the opportunity for PA maintenance.
Social opportunity	Other people and organisations affecting the opportunity for PA maintenance. (e.g. culture and social norms)
Motivation	All the brain processes that energise and direct PA maintenance
Reflective motivation	Analytical decisions, evaluations and plans, conscious intent for PA maintenance (e.g. planning and evaluation)
Automatic motivation	Habitual processes, emotional responding to PA maintenance

Theoretical framework of acceptability themes and interpretation. *Reproduced from.*³

Theme	Interpretation
Affective attitude	How participants feel about the remote coaching intervention
Self-efficacy	The participants' confidence in their ability to follow the advice given during the remote coaching intervention
Perceived effectiveness	The extent to which participants perceive the coaching intervention to be effective (to promote PA maintenance)
Ethicality	The extent to which the remote coaching intervention had good fit with the participants' value system and expectations of it
Intervention coherence	The extent to which the participants understand the aim of the remote coaching intervention
Burden	The perceived amount of effort that was required / the burden to participate in the remote coaching intervention
Opportunity costs	The extent to which benefits, profits or values must be given up to engage in the remote coaching intervention

References

1. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;6:42
2. West R, Michie S. A brief introduction to the COM-B Model of behaviour and the PRIME Theory of motivation [v1]. Qeios 2020.
3. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res* 2017;17(1):88

Appendix 4.2

Interview guide

- Question. Did you receive the remote coaching intervention or not (intervention/control group)?

Part I. Determinants of PA maintenance (all participants)

- Question. What were your experiences with the transition phase from a supervised rehabilitation program to habitual PA in the community?
- Question. How is exercise/PA currently going?

Capability

- Question. To what extent were you able to maintain PA levels and/or exercise independently beyond completion of the supervised rehabilitation program?
- Question. What did you learn during the supervised rehabilitation program (and the remote coaching?)

Opportunity

- Question. In what way did your current living- and social situation influence your PA maintenance?
- Question. Which environmental factors made it easier/more difficult for you to perform PA? What did you perceive as barriers and enablers for PA maintenance?
- Question. What role did (lack of) social support play in PA maintenance? And professional guidance?

Motivation

- Question. To what extent were you motivated for PA maintenance in the past six months? Did this change over time and what motivated you?
- Question. Did you feel confident to perform PA independently?
- Question. Did you perform PA regularly in the past, before you were diagnosed with cancer?
- Question. What are your beliefs about PA benefits?

Part II. Acceptability of remote coaching (participants in the intervention group)

- Question. What were your experiences with the remote coaching intervention?

Affective attitude

- Question. How did you feel about the remote coaching intervention?
- Question. How did you experience the personal contact with the coach?

Self-efficacy

- Question. To what extent were you able to follow the advice given during the remote coaching?
- Question. To what extent did you feel confident about your capability to follow the advices given during the remote coaching?

Perceived effectiveness

- Question. To what extent did you perceive the remote coaching intervention to be effective/beneficial?
- Question. To what extent did the remote coaching intervention help you with PA maintenance? In which way?

Ethicality

- Question. What were your expectations about the remote coaching intervention?
- Question. To what extent did the remote coaching intervention match your expectations?

Intervention coherence

- Question. Could you explain what the aim of the remote coaching intervention was?

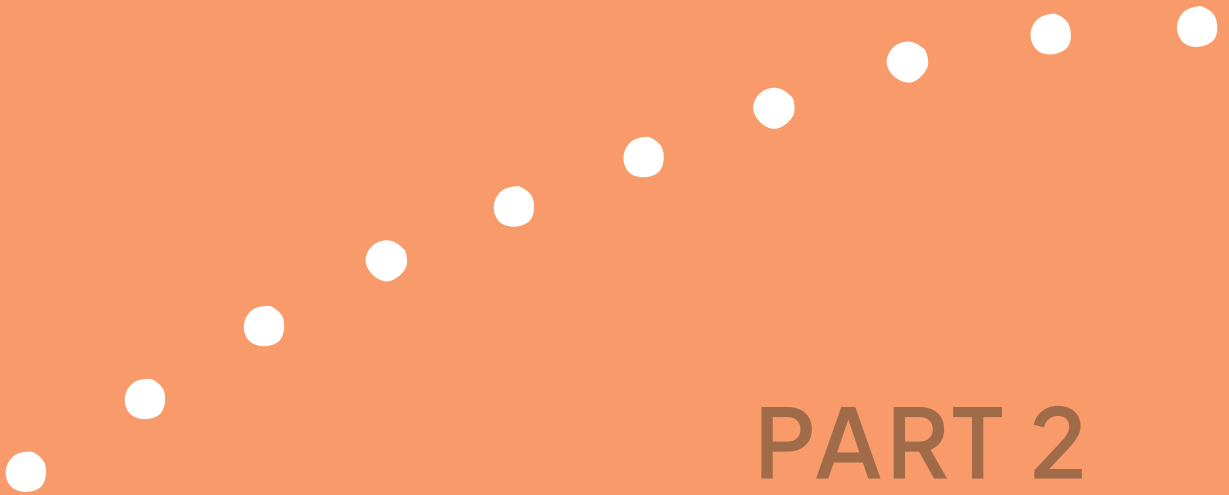
Burden

- Question. To what extent did you experience the remote coaching intervention as a burden?

Opportunity costs

- Question. To what extent did you have to cancel/reschedule other activities to participate in the remote coaching intervention?





PART 2

Monitoring aerobic capacity in cancer survivors



CHAPTER 5

Criterion validity and responsiveness of the steep ramp test to evaluate aerobic capacity in survivors of cancer participating in a supervised exercise rehabilitation program

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Abstract

Objective

To evaluate the criterion validity and responsiveness of the steep ramp test (SRT) compared to the cardiopulmonary exercise test (CPET) in evaluating aerobic capacity in survivors for cancer participating in a rehabilitation program.

Design

A prospective cohort study in which survivors of cancer performed a SRT and CPET before ($T=0$) and after ($T=1$) a 10-week exercise rehabilitation program. Peak work rate achieved during the SRT (SRT-WR_{peak}) was compared with peak oxygen uptake measured during CPET (CPET-VO_{2peak}), which is the criterion standard for aerobic capacity. Correlation coefficients were calculated between SRT-WR_{peak} and CPET-VO_{2peak} at $T=0$ to examine criterion validity and between changes in SRT-WR_{peak} and CPET-VO_{2peak} from $T=0$ to $T=1$ to determine responsiveness. Receiver operating characteristic (ROC) analysis was performed to examine the ability of the SRT to detect a true improvement (6%) in CPET-VO_{2peak}.

Results

An r of 0.86 ($n=106$) was found for the relation between SRT-WR_{peak} and CPET-VO_{2peak} at $T=0$. An r of 0.51 was observed for the relation between changes in SRT-WR_{peak} and CPET-VO_{2peak} ($n=59$). ROC analysis showed an area under the curve of 0.74 for the SRT to detect a true improvement in CPET-VO_{2peak}, with an optimal cut-off value of +0.26 W/kg (sensitivity 70.7%, specificity 66.7%).

Conclusions

As SRT-WR_{peak} and CPET-VO_{2peak} were strongly correlated, the SRT seems a valid tool to estimate aerobic capacity in cancer survivors. The responsiveness to measure changes in aerobic capacity seems moderate. Nevertheless, the SRT seems able to detect improvement in aerobic capacity, with a cut-off value of 0.26 W/kg.

Introduction

Cancer incidence and survival rates are increasing owing to the aging population and improved diagnosis and treatment modalities. This leads to a growing population of cancer survivors, who live longer with the consequences of cancer and its treatment.¹ Current guidelines of the American College of Sports Medicine emphasise the strong level of evidence for the positive effects of exercise on physical functioning, fatigue, anxiety, depression, and health-related quality of life in survivors for cancer.² An important indicator of physical functioning is aerobic capacity, which is defined as the maximum amount of oxygen that can be taken in, transported, and used by the muscles during prolonged exercise.³ Aerobic capacity is dependent on the integrative function of the pulmonary, cardiovascular, and metabolic systems and is considered a good reflection of overall health.⁴ Moreover, aerobic capacity is found to be inversely related to all-cause and cancer-related mortality.^{5,6} Therefore, it is worrying that patients treated for cancer, experience a longstanding decline in aerobic capacity of 5–22%.^{7,8} Accurate measurement of aerobic capacity is important not only for the identification of exercise limitations but also for an adequate individualised prescription of training intensity and for monitoring of training progress.^{9,10}

The criterion standard to examine aerobic capacity is to determine maximal oxygen uptake (VO_2max) during a maximal incremental exercise test with respiratory gas analysis, usually referred to as the cardiopulmonary exercise test (CPET).¹¹ A true VO_2max is achieved when oxygen uptake (VO_2) levels off, despite the continuation of exercise with an increasing work rate.³ In clinical practice, however, this plateau is rarely seen in nonathletic or those with disease. Therefore, the highest VO_2 attained during a maximal, symptom-limited CPET (CPET- VO_2peak) is considered the best available index of aerobic capacity.¹²

Nevertheless, performing a CPET is not always feasible, because the procedures are time-consuming and require advanced equipment, trained staff, and medical supervision.¹⁰ Therefore, accurate, non-sophisticated performance-based tests to evaluate aerobic capacity are needed. The steep ramp test (SRT) is a short maximal exercise test performed on a cycle ergometer, with an increasing work rate of 25 W every 10 seconds until

voluntary exhaustion. De Backer et al.¹³ studied the validity of the SRT to estimate aerobic capacity in 37 survivors for cancer attending an exercise program and found a strong correlation ($r=0.82$) between SRT-WRpeak and CPET-VO₂peak. Similar correlations were found in patients with diabetes, healthy children, and children with cystic fibrosis.^{14–16} To our knowledge, the responsiveness of the SRT to changes in aerobic capacity has not yet been studied, while this is considered to be an important measurement property for performance tests used to monitor training progression and to make necessary program adjustments.

Therefore, the objective of this study was to evaluate the criterion validity and responsiveness of the SRT compared to CPET in evaluating aerobic capacity in survivors of cancer attending a 10-week supervised exercise rehabilitation program. The following *a priori* hypotheses were formulated. First, based on the results of previous studies¹³, the correlation coefficient between CPET-VO₂peak and SRT-WRpeak was expected to be positive and strong (>0.70). Second, based on a larger degree of measurement error that comes along with repeated testing, a moderate correlation (0.50 – 0.70) was expected between the change in CPET-VO₂peak and SRT-WRpeak over time.^{17,18} Third, and for the same reason, the ability of the SRT to discriminate between participants who did or did not improve in aerobic capacity was expected to be moderate. As such, the area under the curve (AUC) of the receiver operating characteristics (ROC) was expected to be in the range of 0.60 to 0.80 .

Methods

Participants

Participants were consecutively recruited from the multidisciplinary oncology rehabilitation program at the Department of Physical Therapy of the Maastricht University Medical Centre+ (MUMC+) between November 2018 and March 2020. This program for survivors of cancer was developed according to national guidelines for oncology rehabilitation.¹⁹ Patients were eligible for the program when they completed active medical treatment and were suffering from physical and psychosocial complaints, as identified by the sports physician, occupational therapist, and psychologist. Contraindications for participation in the rehabilitation program were the

inability to perform basic activities of daily living (e.g., walking) and the presence of disabling comorbidities that seriously hamper physical exercise (e.g., severe heart failure, chronic obstructive pulmonary diseases, neurological or cognitive disorders). The program consisted of a 10-week physical exercise training program, supplemented with treatment by a psychologist and/or occupational therapist when needed. Patients were included in the study when they met the criteria for participation in the rehabilitation program, completed a CPET and SRT before the start of the exercise program, and gave written informed consent for the use of their usual care data. Participants were excluded for analysis when they were unable to cycle until voluntary exhaustion during one or both exercise tests. Procedures of data collection were in compliance with the Declaration of Helsinki and were approved by the medical ethics committee of the MUMC+ (registration number 2018-0648). This study was reported according to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines.²⁰

Exercise program

Participants completed a 10-week supervised exercise program to improve aerobic capacity and muscle strength as part of the multidisciplinary oncology rehabilitation program. The program consisted of two training sessions per week, which both started with one hour of combined endurance and resistance training, followed by 30 minutes of rest and, subsequently, 30 minutes of varying sports activities in the sports hall or swimming pool. Training intensity of the first part of the program was personalised. To determine the intensity of the resistance training, a submaximal repetition maximum test was performed on each exercise machine to calculate the true 1-repetition maximum. Participants performed 4 strength exercises each session, targeting large muscle groups of the upper body, lower body, and core. Resistance training consisted of 3 sets of 8-12 repetitions, at a training intensity of 60% of the participant's one-repetition maximum. Endurance training in the first training session of the week consisted of 20 minutes walking on a treadmill, with a walking speed of 80% of their speed that was achieved during a baseline 6-minute walking test. In the other training session, participants performed 2 sets of 10 minutes interval training on a cycle ergometer, one set before and one after the resistance training program. Intervals were performed for 60 seconds and 30 seconds at 30% and 65% of the participant's SRT-WRpeak,

respectively.¹³ A moderate to high exercise intensity was pursued for all training components, corresponding with a 0–10 Borg rating of perceived exertion of 4–6. Training load was adjusted weekly to achieve this.

Test procedures

Participants performed a CPET and SRT before the start of the exercise program (T=0) and after 10 weeks of exercise training (T=1). CPET was performed to check for cardiopulmonary comorbidities and contraindications to exercise training, and to assess aerobic capacity. The SRT was performed for the interval-training prescription, as described by de Bakker et al.¹³ The CPET and SRT were planned separately, with a between-visit time of 2 to 7 days. Planning of the CPET and the SRT had to be adapted to the rehabilitation trajectory of the patient, because both tests were part of usual care for all patients participating in the oncology rehabilitation program. Therefore, test order was SRT-CPET at T=0 and CPET-SRT at T=1. Seat height was adjusted to the participant's leg length and the same seat height was used for both tests at T=0 and T=1. Participants were blinded for test outcomes during all tests. The CPET and SRT were performed independently and researchers were blinded for previous test outcomes.

Steep ramp test

The SRT was performed on an electronically braked cycle ergometer (Lode Corival, Lode BV, the Netherlands). Participants started with a 3-minute warming-up phase with a work rate of 25 watts. After this, the work rate was increased by 25 watts per 10 seconds in a ramp-like manner. Participants were instructed to keep cycling until exhaustion, with a pedalling frequency of at least 60 rotations per minute (rpm). Peak exercise was defined as the point where the pedal frequency dropped below 60 rpm despite strong verbal encouragement. Voluntary exhaustion was considered to be achieved when participants showed clinical signs of intense effort (e.g., unsteady biking, sweating, and clear unwillingness to continue exercising). SRT-WR_{peak} was expressed in watts per kg bodyweight and was determined as the highest achieved work rate at peak exercise (W/kg).

Cardiopulmonary exercise test

Anthropometric measurements were conducted before the CPET. After brief pretest instructions, baseline cardiopulmonary values were collected

during a two-minute rest period while seated at a cycle ergometer (Lode Corival, Lode BV, the Netherlands). After the rest period, the participant completed a 3-minute warm-up phase of unloaded cycling. Subsequently, the work rate started to increase by an incremental ramp protocol adjusted to the patient's self-reported physical activity level, aimed at reaching a maximal effort within 8 to 12 minutes. Participants were instructed to keep cycling until exhaustion, with a pedalling frequency of at least 60 rpm. The protocol continued until the patient stopped cycling or pedalling frequency fell below 60 rpm, despite strong verbal encouragement. Continuous breath-by-breath analysis was obtained during the test using an ergospirometry system calibrated for respiratory gas analysis measurements and volume measurements (Vyntus CPX, CareFusion, Netherlands). Peak exercise was defined as the point where the pedalling frequency dropped below 60 rpm. Respiratory gas analysis values at peak exercise were calculated as the average value over the last 30 seconds before test termination. Similar to the SRT, voluntary exhaustion was considered to be achieved when participants showed clinical signs of intense effort.

Statistical analysis

Statistical analyses were done using SPSS version 23.0. Continuous variables were checked for normality using histograms and Q-Q plots. Patient characteristics and exercise test outcomes were presented as mean $\pm$ SD or as median and interquartile ranges (IQR) for continuous variables, as appropriate, whereas data of categorical variables were expressed as frequencies and percentages. Criterion validity of the SRT was evaluated for all participants at T=0 using Pearson's or Spearman's correlation coefficient, as appropriate, with corresponding 95% confidence intervals (CIs) to quantify the relationship between SRT-WR_{peak} and CPET-VO_{2peak}. To evaluate the responsiveness of the SRT, the correlation coefficient with corresponding 95% CI was calculated between the absolute change in SRT-WR_{peak} and CPET-VO_{2peak} from T=0 to T=1, for participants who completed the exercise tests at both time points. Receiver operating characteristic (ROC) curves were plotted between the dichotomised change in CPET-VO_{2peak} (improvement versus no improvement) and the absolute change in SRT-WR_{peak}. The minimal detectable change for improvement in CPET-VO_{2peak} was defined as a relative increase of $\geq 6\%$.²¹ The area under the curve (AUC) of the ROC curve

with corresponding 95% CI was calculated to evaluate the ability of the SRT to detect a true improvement in CPET-VO₂peak of $\geq 6\%$ over time. The Youden index (sensitivity + specificity - 1) was calculated for all points of the ROC curve. The highest value was selected as a potential cutoff point to indicate the minimal detectable change in CPET-VO₂peak. When the sensitivity for this cutoff point was $< 70.0\%$, a second cut-off value was chosen at the highest Youden index where the sensitivity was $\geq 70.0\%$, because sufficient sensitivity is required to detect training progression. Sensitivity, specificity, and predictive values (%) were calculated for the cut-off value(s).

Results

Participant characteristics

Of the 116 patients who were eligible to participate, 106 (91.4%) were included in the analysis. Seven patients (6.0%) dropped out because they were unable to complete one or both of the exercise tests until voluntary exhaustion at T=0. One patient was excluded because of a surgical intervention between the CPET and SRT at T=0. Test results at T=1 were available for 59 participants (55.7%). For 31 of the 47 participants (66.0%) who were lost to follow-up, the rehabilitation program and the tests at T=1 were postponed or cancelled due to the COVID-19 pandemic, during which all outpatient activities were cancelled for four months. This period was too long for the purpose of this study; therefore, no catch-up measurements were undertaken for these participants. See Figure 5.1 for a flowchart of participant inclusion. The final sample consisted of 78 women (73.6%) and 28 men (26.4%). Mean age was 56.6 ± 11.0 years and breast cancer was the most prevalent diagnosis (48.1%). Further baseline characteristics are summarised in Table 5.1 for all participants (n=106) and for those who completed both exercise tests at T=0 and T=1 (n=59).

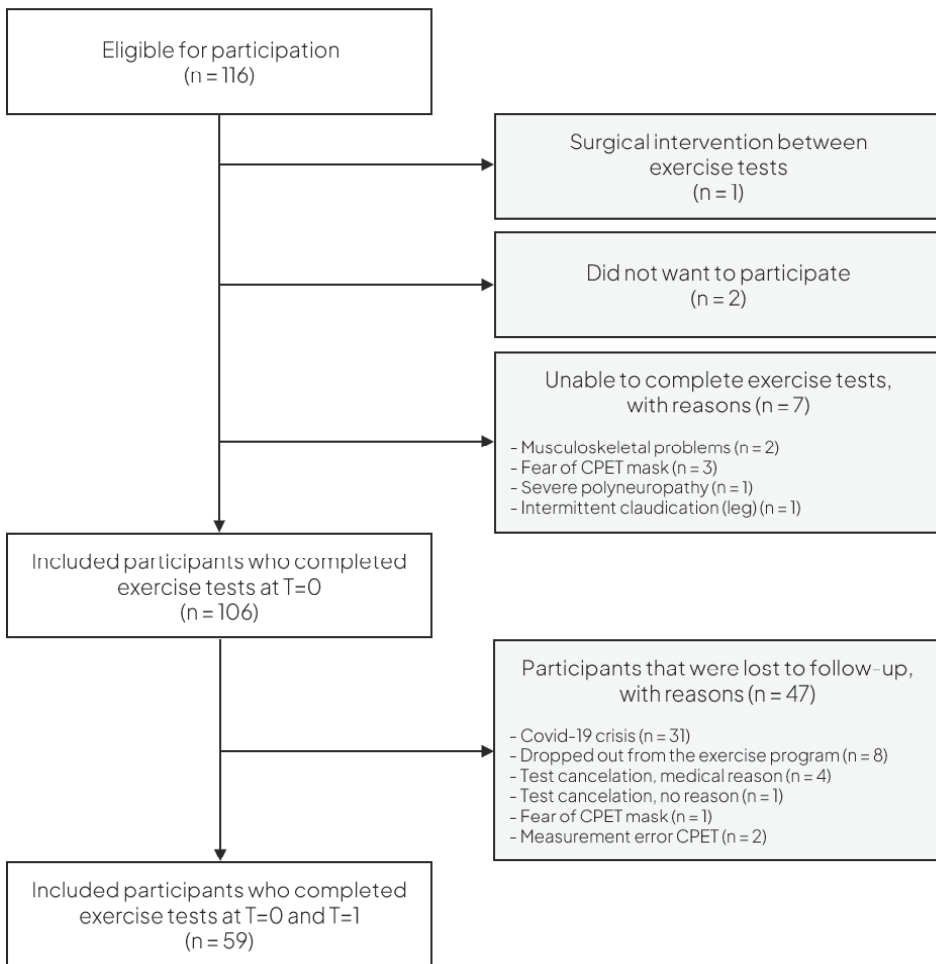


Figure 5.1. Flowchart of participant inclusion. Covid-19 = Coronavirus-19 pandemic.

Table 5.1. Baseline characteristics of the participants.

	Participants who completed tests at T=0 (n=106)	Participants who completed tests at T=0 and T=1 (n=59)
Sex (n)		
Male	28 (26.4)	16 (27.1)
Female	78 (73.6)	43 (72.9)
Age (years)	56.6 ± 11.0	54.6 ± 11.0
Body height (cm)	169.6 ± 7.9	170.3 ± 8.1
Body mass (kg)	79.0 ± 13.8	79.1 ± 12.1
Body mass index (kg/m ²)	27.5 ± 4.8	27.4 ± 4.7
Cancer type (n)		
Breast cancer	51 (48.1)	30 (50.8)
Colorectal cancer	9 (8.5)	3 (5.1)
Lung cancer	7 (6.6)	3 (5.1)
Lymphomas	6 (5.7)	4 (6.8)
Prostate cancer	4 (3.8)	2 (3.4)
Other	29 (27.4)	17 (28.8)
Metastasis (n)		
No metastasis	77 (72.6)	45 (76.3)
Lymphatic metastasis	17 (16.0)	9 (15.3)
Hepatic metastasis	5 (4.7)	2 (3.4)
Skeletal metastasis	4 (3.8)	1 (1.7)
Other	3 (2.8)	2 (3.4)
Treatment (n)		
Surgery	80 (75.5)	47 (79.7)
Chemotherapy	62 (58.5)	33 (55.9)
Radiotherapy	55 (51.9)	26 (44.1)
Hormone therapy	32 (30.2)	20 (33.9)
Immunotherapy	11 (10.4)	7 (11.9)
Stem cell transplantation	4 (3.8)	2 (3.4)

Values are presented as n (%) for categorical variables and as mean ± SD for continuous variables.

Exercise test outcomes

SRT-WRpeak and CPET-VO₂peak are presented in Table 5.2 for all participants at T=0 (n=106) and for the participants who completed both tests at T=0 and T=1 (n=59), with corresponding change scores. Mean ± SD was 3.0 ± 0.9 W/kg for SRT-WRpeak and 19.5 ± 5.2 mL/kg/min for CPET-VO₂peak at T=0. Median (IQR) between-visit time for the SRT and CPET was 5 (2) days at T=0 and 7 (5) days at T=1. Participants who completed both tests at T=0 and T=1 showed a mean change of 0.4 ± 0.3 W/kg (+12.9%) on the SRT-WRpeak and a mean change of 2.0 ± 2.3 mL/kg/min (+10.0%) on the CPET-VO₂peak after completion of the exercise program. Forty-one

participants (69.5%) showed a relative increase of $\geq 6\%$ in CPET-VO₂peak and thus a true improvement in aerobic capacity.

Table 5.2. Exercise test outcomes.

	Participants who completed tests at T=0 (n=106)	Participants who completed tests at T=0 and T=1 (n=59)			
		T=0	T=1	Change	%change
SRT-WRpeak (W/kg)	3.0 ± 0.9	3.1 ± 0.9	3.5 ± 1.0	0.4 ± 0.3	12.9
SRT duration (min:s)	01:30 ± 00:25	01:33 ± 00:25	01:48 ± 00:26		
CPET-VO ₂ peak (mL/kg/min)	19.5 ± 5.2	20.1 ± 5.3	22.1 ± 6.3	2.0 ± 2.3	10.0
CPET test duration (min:s)	09:43 ± 01:35	09:49 ± 01:31	11:01 ± 02:07		

Values are presented as mean ± SD. SRT test duration and CPET test duration is the duration of loaded cycling during these tests and is expressed in minutes and seconds. SRT=steep ramp test; CPET=cardiopulmonary exercise test; SRT-WRpeak=peak work rate achieved at the steep ramp test; CPET-VO₂peak=peak oxygen uptake achieved at the cardiopulmonary exercise test.

Validity and responsiveness

A Pearson's r of 0.86 (95% CI 0.80 ; 0.90) was found for the relation between SRT-WRpeak and CPET-VO₂peak at T=0 (Figure 5.2). A Pearson's r of 0.51 (95% CI, 0.29 ; 0.68) was found for the relation between individual change scores in SRT-WRpeak and the CPET-VO₂peak from T=0 to T=1 (Figure 5.3). ROC analysis showed an AUC of 0.74 (95% CI 0.60 ; 0.87) of the SRT to discriminate between participants who did or did not improve in aerobic capacity (increase in CPET-VO₂peak $\geq 6\%$) following the rehabilitation program (Figure 5.4). The maximal value of the Youden index was found at 0.38 W/kg, which therefore was chosen as a potential cutoff value. Using this cutoff value resulted in a sensitivity of 56.1%, a specificity of 83.3%, a positive predictive value (PPV) of 88.5%, and a negative predictive value (NPV) of 45.5%. A second value was chosen, aiming for a sensitivity $\geq 70.0\%$. The highest Youden index for a sensitivity $\geq 70.0\%$ was found at 0.26 W/kg, which therefore was chosen as the optimal cutoff point of the SRT to detect a true improvement in aerobic capacity. When using this cutoff value in the sample, 35 participants (58.3%) improved aerobic capacity according to the SRT. This resulted in a sensitivity of 70.7%, a specificity of 66.7%, a PPV of 82.9%, and an NPV of 50.5% (Table 5.3).

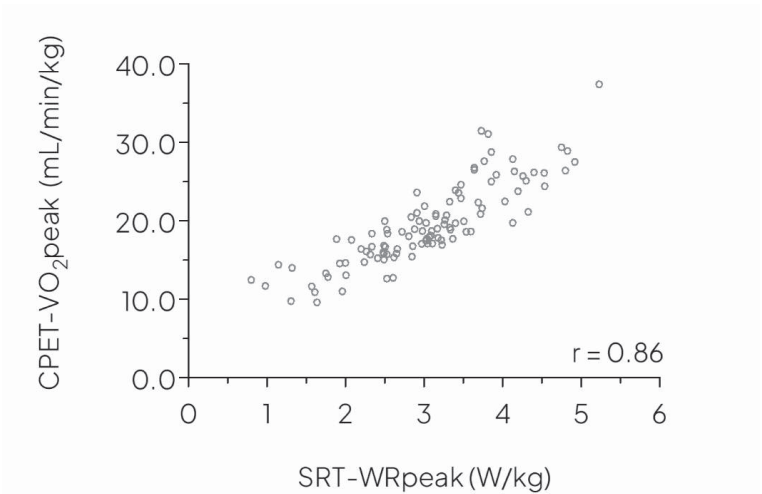


Figure 5.2. Scatterplot for the relationship between SRT-WRpeak and CPET-VO₂peak with the corresponding Pearson's correlation coefficient (r); SRT-WRpeak=peak work rate achieved during the steep ramp test; CPET-VO₂peak=peak oxygen uptake attained at the cardiopulmonary exercise test.

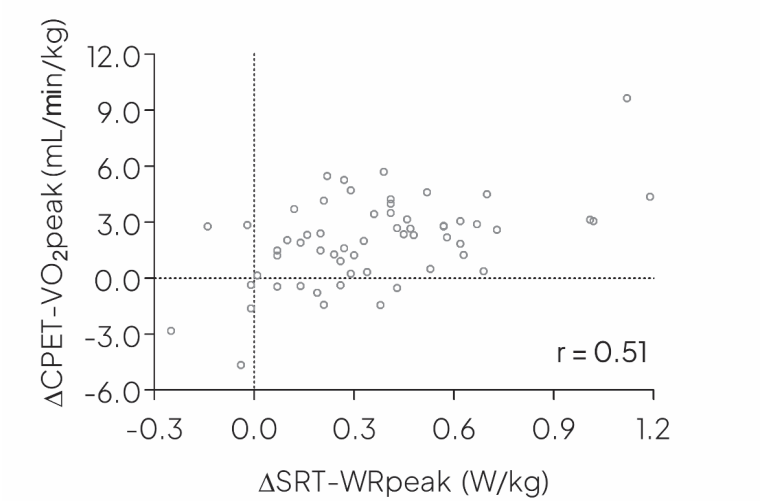


Figure 5.3. Scatterplot for the relationship between change over time (Δ) in SRT-WRpeak and CPET-VO₂peak with the corresponding Pearson's correlation coefficient (r). SRT-WRpeak=peak work rate achieved during the steep ramp test; CPET-VO₂peak=peak oxygen uptake attained at the cardiopulmonary exercise test.

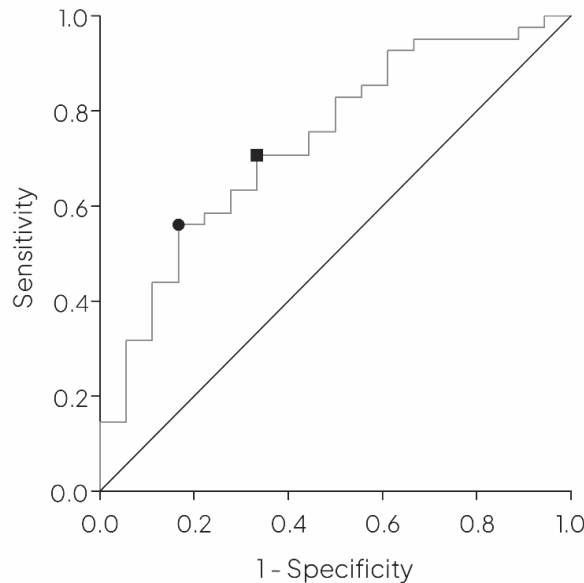


Figure 5.4. ROC curve for the ability of the SRT to detect a true improvement in CPET-VO₂peak. Potential cutoff values are displayed in the graph. ●: cutoff value of 0.38 W/kg, which has a sensitivity lower than 70.0%. ■: optimal cutoff value of 0.26 W/kg. ROC=receiver operating characteristic.

Table 5.3. Sensitivity, specificity, and predictive values of the SRT to detect improvement in aerobic capacity.

SRT cutoff value (W/kg)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.38 *	56.1	83.3	88.5	45.5
0.26 †	70.7	66.7	82.9	50.0

*The cutoff value with the highest Youden index; † The cutoff value with the highest Youden index with a sensitivity $\geq 70.0\%$. SRT=steep ramp test; PPV=positive predictive value; NPV=negative predictive value."

Discussion

The objective of this study was to examine the criterion validity and responsiveness of the SRT to evaluate aerobic capacity in survivors of cancer. Three a priori hypotheses were formulated. Pearson's correlation analysis showed a strong relationship ($r=0.86$) between SRT-WRpeak and CPET-VO₂peak at T=0. This indicates that the SRT has a good validity to measure aerobic capacity, confirming the first hypothesis. These findings

are similar to the results of de Backer et al., who found an r of 0.82 between SRT-WR_{peak} and CPET-VO_{2peak}.¹³ The SRT seemed to be a valid measurement tool in previous studies with other populations as well.^{14–16} These findings are promising, since the SRT is a practical test, which is less expensive and time-consuming than CPET and can be performed without medical supervision. However, CPET in cancer survivors is not only used as a test to measure aerobic capacity, but also for the assessment of exercise-limiting factors and exercise-induced cardiovascular risk.¹⁹ Because this information cannot be obtained during the SRT, it is not recommended to use the SRT as an alternative for CPET in cancer survivors with increased cardiovascular risks, such as pre-existent cardiovascular disease, treatment with cardiotoxic chemotherapy, and left-sided chest radiation.⁸ Yet, the SRT can be used to provide insight in the aerobic capacity of survivors of cancer and to personalize physical exercise training program prescription.

A moderate correlation was found between change in SRT-WR_{peak} and CPET-VO_{2peak} ($r=0.51$), which is in agreement with the second hypothesis. This indicates that the SRT has a moderate responsiveness and might not be the most accurate tool to measure change in aerobic capacity. The current study was the first to examine the responsiveness for aerobic capacity of the SRT. However, a prediction model that was developed by the Bakker et al.¹³ and extended and externally validated by Stuiver et al.²² to predict aerobic capacity in individual cancer patients based on the SRT, showed acceptable results at group level but was insufficiently accurate to estimate CPET-VO_{2peak} in individual patients. This is in accordance with the current findings of a moderate responsiveness, because responsiveness is a measurement property of agreement between individual changes over time.¹⁸

The third and last hypothesis was aimed at testing the ability of the SRT to discriminate between participants who did or did not improve in CPET-VO_{2peak}. An AUC of 0.60–0.80 was expected and results confirmed this. Results showed an AUC of 0.74 which implicates that the SRT is sufficiently responsive to indicate a true improvement in aerobic capacity over time.²³ The maximal value of the Youden index was found at 0.38 W/kg; however, using this cutoff value would result in a low sensitivity (56.1%). Because positive feedback is a strong motivator during rehabilitation, the number of false negatives of a performance test should be minimised. Therefore, a

sensitivity of 70.0% was pursued, which resulted in an optimal cutoff point of an improvement in SRT performance of 0.26 W/kg to detect a true improvement in CPET-VO₂peak (≥6%).

For both the SRT and CPET, a maximal effort was considered to be reached when participants showed clinical signs of voluntary exhaustion, which is a subjective criterion. An objective criterion that is often used to confirm a maximal effort at the CPET is a respiratory exchange rate at peak exercise (RERpeak) ≥1.10.²⁴ After analysing the study data, it was noticed that not all patients performed a maximal effort at the CPET, according to the RERpeak criterion. These findings are in agreement with several other studies in cancer survivors, which also show that a RERpeak ≥1.10 is often not reached in this population.^{25,26} To elucidate whether this influenced our results concerning the validity and responsiveness of the SRT, we performed a post-hoc analysis. As such, a subgroup of patients who met the RERpeak criterion and a subgroup of patients who did not meet this objective criterion were created.

Mean ± SD RERpeak was 1.16 ± 0.09 in the total sample (n=106) at T=0. Post-hoc analysis showed that 77 participants (72.6%) reached an RERpeak ≥1.10 at T=0. Participants who did not achieve an RERpeak ≥1.10 at T=0 (n=29, 27.4%), reached an RERpeak ranging from 0.96 to 1.09. Mean ± SD RERpeak was 1.17 ± 0.10 at T=0 and 1.18 ± 0.10 at T=1 in the group of participants (n = 59) who completed CPETs at T=0 and T=1. The post-hoc analysis demonstrated that 42 of these participants (71.2%) reached an RERpeak ≥1.10 during both CPETs. Since objective criteria for a maximal effort do not exist for the SRT, the heart rate at peak exercise (HRpeak) during the SRT was compared between the SRTs at T=0 and T=1. Participants who completed the SRT at T=0 and T=1, reached a mean HRpeak of respectively 137 ± 23 bpm and 140 ± 22 bpm. These results demonstrate only minor differences between T=0 and T=1 in RERpeak and HRpeak at the SRT and CPET, respectively. Therefore, it can be assumed that participants showed equal levels of effort during the SRT and CPET tests at T=0 and T=1.

Subsequently, validity and responsiveness analyses were repeated in the subgroup of participants that met the criteria of an RERpeak ≥1.10 at the CPETs. For validity, this post-hoc analysis showed an r of 0.84 for the relation between SRT-WRpeak and CPET-VO₂peak at T=0. For

responsiveness, an r of 0.50 was found for the relation between individual change scores of SRT-WR_{peak} and CPET-VO_{2peak}. ROC analysis showed an AUC of 0.74. These results are similar to the original study results, in which all participants who showed voluntary exhaustion were included, even if they failed to reach an RER_{peak} ≥ 1.10 . As such, it appeared that the delivered effort, based on the objective RER_{peak} criterion, did not affect the study results.

Study limitations

One study limitation was the fact that the test order was not randomised. Randomisation could not be performed since the CPET and SRT were part of usual care and had to be adapted to the rehabilitation trajectory of the patient. Consequently, day-to-day performance variation could have influenced the results of the validity and responsiveness of the SRT.

Conclusion

Results suggest that the SRT is a valid tool to estimate aerobic capacity in cancer survivors. Moderate correlations between change scores indicate that the SRT has a limited responsiveness to measure changes in aerobic capacity. Nevertheless, ROC analysis implicates that the SRT is able to determine whether aerobic capacity has truly improved with a cutoff point of 0.26 W/kg.

References

1. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016;66(4):271-289.
2. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
3. Hill AV, Lupton H. Muscular Exercise, Lactic Acid, and the Supply and Utilization of Oxygen. *QJM: An International Journal of Medicine* 1923;os-16(62):135-171.
4. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* 2016;134(24):e653-e699.
5. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing. *JAMA Netw Open* 2018;1(6):e183605.
6. Vainshelboim B, Muller J, Lima RM, Nead KT, Chester C, Chan K, et al. Cardiorespiratory fitness, physical activity and cancer mortality in men. *Prev Med* 2017;100:89-94.
7. Hurria A, Jones L, Muss HB. Cancer Treatment as an Accelerated Aging Process: Assessment, Biomarkers, and Interventions. *Am Soc Clin Oncol Educ Book* 2016;35: e516-e522.
8. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;30(20):2530-2537.
9. Winters-Stone KM, Neil SE, Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br J Sports Med* 2014;48(12):987-995.
10. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol* 2008;9(8):757-765.
11. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(10):1451; author reply.
12. Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ. The maximally attainable VO₂ during exercise in humans: the peak vs. maximum issue. *J Appl Physiol* (1985) 2003;95(5): 1901-1907.
13. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil* 2007;88(5):610-616.
14. Rozenberg R, Bussmann JB, Lesaffre E, Stam HJ, Praet SF. A steep ramp test is valid for estimating maximal power and oxygen uptake during a standard ramp test in type 2 diabetes. *Scand J Med Sci Sports* 2015;25(5):595-602.
15. Bongers BC, de Vries SI, Helders PJ, Takken T. The steep ramp test in healthy children and adolescents: reliability and validity. *Med Sci Sports Exerc* 2013;45(2):366-371.
16. Bongers BC, Werkman MS, Arets HG, Takken T, Hulzebos HJ. A possible alternative exercise test for youths with cystic fibrosis: the steep ramp test. *Med Sci Sports Exerc* 2015;47(3):485-492.
17. Hopkins WG. Measures of reliability in sports medicine and science. *Sports Med* 2000;30(1):1-15.
18. De Vet HC, Bouter LM, Bezemer PD, Beurskens AJ. Reproducibility and responsiveness of evaluative outcome measures: theoretical considerations illustrated by an empirical example. *Int J Technol Assess Health Care* 2001;17(4):479-487.
19. National Cancer Institute. Dutch Cancer Rehabilitation Guidelines. 2017.

20. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010;19(4):539-549.
21. Keteyian SJ, Brawner CA, Ehrman JK, Ivanhoe R, Boehmer JP, Abraham WT, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise parameters: implications for clinical trials and clinical practice. *Chest* 2010;138(4):950-955.
22. Stuiver MM, Kampshoff CS, Persoon S, Groen W, van Mechelen W, Chinapaw MJM, et al. Validation and Refinement of Prediction Models to Estimate Exercise Capacity in Cancer Survivors Using the Steep Ramp Test. *Arch Phys Med Rehabil* 2017;98(11):2167-2173.
23. De Vet HC, Terwee CB, Mokkink LB, Knol DL. *Measurement in medicine: a practical guide*. Cambridge University Press; 2011.
24. Steins Bisschop CN, Velthuis MJ, Wittink H, Kuiper K, Takken T, van der Meulen WJ, et al. Cardiopulmonary exercise testing in cancer rehabilitation: a systematic review. *Sports Med* 2012;42(5):367-379.
25. Santa Mina D, Au D, Papadopoulos E, O'Neill M, Diniz C, Dolan L, et al. Aerobic capacity attainment and reasons for cardiopulmonary exercise test termination in people with cancer: a descriptive, retrospective analysis from a single laboratory. *Supportive Care in Cancer* 2020;1-10.
26. Canada JM, Trankle CR, Carbone S, Buckley LF, Chazal M, Billingsley H, et al. Determinants of Cardiorespiratory Fitness Following Thoracic Radiotherapy in Lung or Breast Cancer Survivors. *Am J Cardiol* 2020;125(6):988-996.



CHAPTER 6

Monitoring aerobic capacity in cancer survivors
using self-reported questionnaires:
criterion validity and responsiveness

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Abstract

Background

Evaluating the criterion validity and responsiveness of the self-reported FitMáx©-questionnaire, Duke Activity Status Index (DASI), and Veterans Specific Activity Questionnaire (VSAQ) to monitor aerobic capacity in cancer survivors.

Methods

Cancer survivors participating in a 10-week supervised exercise program were included. The FitMáx©-questionnaire, DASI, VSAQ, and a cardiopulmonary exercise test (CPET) were completed before (T_0) and after (T_1) the program. Intraclass correlation coefficients (ICC) were calculated between VO_{2peak} estimated by the questionnaires (questionnaire- VO_{2peak}) and VO_{2peak} measured during CPET (CPET- VO_{2peak}), at T_0 to examine criterion validity, and between changes in questionnaire- VO_{2peak} and CPET- VO_{2peak} (ΔT_0 - T_1) to determine responsiveness. Receiver operating characteristic (ROC) analyses were performed to examine the ability of the questionnaires to detect true improvements ($\geq 6\%$) in CPET- VO_{2peak} .

Results

Seventy participants were included. Outcomes at T_1 were available for 58 participants (83%). Mean CPET- VO_{2peak} significantly improved at T_1 ($\Delta 1.6$ mL/min/kg or 8%). Agreement between questionnaire- VO_{2peak} and CPET- VO_{2peak} at T_0 was moderate for the FitMáx©-questionnaire (ICC=0.69) and VSAQ (ICC=0.53), and poor for DASI (ICC=0.36). Poor agreement was found between Δ CPET- VO_{2peak} and Δ questionnaire- VO_{2peak} for all questionnaires (ICC of 0.43, 0.19 and 0.18 for the FitMáx©-questionnaire, VSAQ, and DASI, respectively). ROC analysis showed that the FitMáx©-questionnaire was able to detect improvements in CPET- VO_{2peak} (area under the curve, AUC=0.77) when using a cut-off value of 1.0 mL/min/kg, while VSAQ (AUC=0.66) and DASI (AUC=0.64) could not.

Conclusion

The self-reported FitMáx©-questionnaire has sufficient validity to estimate aerobic capacity in cancer survivors at group level. The responsiveness of the FitMáx©-questionnaire for absolute change is limited, but the questionnaire is able to detect whether aerobic capacity improved. The FitMáx©-questionnaire showed substantially better values of validity and responsiveness compared to DASI and VSAQ.

Introduction

Cancer and its medical treatment often lead to impairments in aerobic capacity and consequently decreased physical functioning and health-related quality of life. Literature suggests that low aerobic capacity is associated with increased risks for cancer recurrence and all-cause and cancer-related mortality.^{1,2} Therefore, it is worrying that cancer survivors experience a longstanding decline in aerobic capacity of 5-22% during the course of their treatment.^{3,4} This decline in aerobic capacity can be countered or prevented, and it is well-known that physical exercise is an effective way to do so.^{5,6}

The criterion standard to evaluate aerobic capacity is measuring peak oxygen uptake (VO_2peak) during an incremental maximal exercise test with respiratory gas analysis, also referred to as a cardiopulmonary exercise test (CPET).⁷ Measuring VO_2peak is of great additional value for pre-operative risk-screening, personalised exercise prescription, and monitoring aerobic capacity in patients with cancer.^{8,9} Moreover, CPET is used for exercise pre-participation health screening and to determine the underlying cause of exercise limitation.^{9,10} However, performing CPET is costly, time-consuming, a burden to the patient, and requires costly advanced equipment, and medical supervision.⁹ In many clinical circumstances the main aim is to assess aerobic capacity, without underlying diagnostic question on exercise limitation. Patient-reported outcome measures (PROMs), such as self-reported questionnaires, could be a useful alternative to estimate and monitor aerobic capacity in these settings where a CPET is not feasible or necessary.

The Duke Activity Status Index (DASI) and Veterans Specific Activity Questionnaire (VSAQ) are self-reported questionnaires which are often used in clinical healthcare for the assessment of aerobic capacity in patients.^{11,12} The DASI was developed to assess physical functioning in cardiovascular patients and shows good validity compared to VO_2peak measured during CPET (CPET- VO_2peak) when administered by an interviewer, and moderate validity when self-reported.¹¹ In a recent study with patients scheduled for major cancer surgery, VO_2peak estimated using the DASI (DASI- VO_2peak) showed substantial bias with wide 95% limits of agreement (95% LoA) when compared to CPET- VO_2peak .¹³ The VSAQ was

developed to estimate aerobic capacity in American Veterans describing activities of increasing metabolic equivalent of a task (MET) and showed a moderate correlation with METs derived from CPET.¹² One MET is considered equal to 3.5 mL/kg/min and can be used interchangeably with VO₂peak.¹⁴ In a more recent study with healthy adults, VO₂peak estimated using the VSAQ (VSAQ-VO₂peak) also showed considerable bias with wide 95%-LoA.¹⁵ Although VSAQ and DASI showed a significant correlation with measured VO₂peak, agreement was suboptimal. Besides, both questionnaires were developed and validated in an American population. A major drawback of the VSAQ is the use of activities, such as basketball and skiing, which are not practiced globally.¹⁶

More recently, the FitMáx®-questionnaire, hereafter called FitMáx, was developed as a self-reported questionnaire to estimate VO₂peak (FitMáx-VO₂peak) in the general Dutch population. FitMáx-VO₂peak is based on the self-reported maximum capacity of walking, stair climbing, and cycling combined with age, sex, and body mass index (BMI). In a recent study, the FitMáx showed a strong intraclass correlation (ICC=0.93) with CPET-VO₂peak, and acceptable bias (-0.24 with 95% LoA -9.23 ; 8.75), in a heterogeneous group of 228 patients (with lung, cardiac and oncologic diseases) and athletes. The results for FitMáx were compared with DASI (ICC=0.62, bias of 3.32 with 95% LoA -14.81 ; 21.44) and VSAQ (ICC=0.87, bias of 3.44 with 95% LoA -10.11 ; 16.98) in the same population and showed better agreement with CPET-VO₂peak.¹⁷

The clinical usefulness and applicability of PROMs depend on several measurement properties including validity, responsiveness, and reliability. Assessing the responsiveness of an instrument is important to determine whether it is able to detect changes over time. However, no studies regarding the responsiveness of these self-reported questionnaires have been performed before. Therefore, the aim of this study was to assess and compare the 1) population specific criterion validity and 2) responsiveness of VO₂peak predicted by FitMáx, DASI, and VSAQ as self-reported questionnaires, to evaluate aerobic capacity in cancer survivors who participated in a 10-week supervised exercise program.

We hypothesised the population specific agreement between CPET-VO₂peak and FitMáx-VO₂peak at T₀ to be moderate-to good, with an ICC of

>0.70 ;¹⁷⁻¹⁹ and the ICC between change over time in CPET-VO₂peak and FitMáx-VO₂peak to be between 0.40 and 0.60.^{20,21} Furthermore, the ability of the FitMáx to discriminate between participants who did or did not improve in aerobic capacity was expected to be moderate. As such, the area under the curve (AUC) of the receiver operating characteristic curve (ROC-curve) was expected to be in the range of 0.60–0.80.¹⁸ Lastly, looking at the results of previous studies, the validity and responsiveness of FitMáx-VO₂peak in this population are expected to be better compared to the validity and responsiveness of the DASI-VO₂peak and VSAQ-VO₂peak, which are expected to show poor-to moderate agreement with CPET-VO₂peak (ICC <0.70).^{11,17,22}

Methods

Setting

Patients who were scheduled to participate in a supervised exercise program as part of usual-care multidisciplinary oncology rehabilitation were prospectively recruited at the Department of Physical Therapy of the Maastricht University Medical Centre (MUMC+) between January 2021 and December 2021. The multidisciplinary rehabilitation program consisted of a 10-week supervised physical exercise program, supplemented with psychological and/or occupational therapy when indicated. The exercise program consisted of combined endurance and resistance training as described elsewhere.²³ Data collection procedures were in compliance with the Declaration of Helsinki²⁴ and were approved by the medical ethics committee of the MUMC+ (registration number METC 2020-2300). This study was reported according to the Consensus-Based Standards for the Selection of Health Measurement Instruments guidelines (COSMIN).²⁵ The study was registered as NL8568 in the Netherlands Trial Register (<https://trialssearch.who.int>).

Participants

Patients were eligible to participate in the rehabilitation program when they were suffering from physical and psychosocial complaints and/or fatigue due to cancer (treatments). Patients were excluded from participation when they were unable to perform basic activities of daily living (e.g. walking) and

suffered from disabling comorbidities that seriously hamper physical exercise.²³ Within two weeks before the start (T_0) and after the 10-week exercise program (T_1) a CPET was conducted as part of usual care. Patients were included in this study when they were willing to complete three self-reported questionnaires during both CPET consultations and gave written informed consent for the use of their questionnaire and CPET data. Patients who were unable to read and understand the questionnaires, or did not show signs of voluntary exhaustion during the CPET at T_0 (e.g. due to injuries or joint complaints) were excluded from the study.

Test procedures

Anthropometric measurements were conducted before the CPET. After pre-test instructions, baseline cardiopulmonary values were collected during a 2-minute rest period while seated at the cycle ergometer (Lode Corival, Lode BV, Groningen, The Netherlands). After the rest period, the participant completed a 3-minute warm-up phase of unloaded cycling. Subsequently, the work rate started to increase by an incremental maximal ramp protocol adjusted to the patient's self-reported physical activity level (assessed by the sports physician independently from the questionnaire results), aimed to reach a maximal effort within 8–12 minutes.^{26,27} At T_1 , the same ramp protocol was applied for CPET as at T_0 . Participants were instructed to keep cycling until exhaustion, with a pedalling frequency of at least 60 rotations per minute. The protocol continued until the patient stopped cycling or pedalling frequency fell below 60 rotations per minute, despite verbal encouragement. Continuous breath-by-breath analysis was obtained during the test using an ergospirometry system (Vyntus CPX, CareFusion, Netherlands) calibrated for respiratory gas analysis and volume measurements. Peak exercise was defined as the point where the pedalling frequency dropped below 60 rotations per minute. Voluntary exhaustion was considered to be achieved when participants showed clinical signs of intense effort (e.g., unsteady biking, sweating or clear unwillingness to continue exercising). True maximal effort was considered to be reached if one of the two following criteria was met: i) percentage of age-related predicted maximal heart rate and ii) age-related peak respiratory exchange rate (RERpeak).^{28,29} Participants were blinded for test outcomes during both test moments and for questionnaire answers at T_0 , during T_1 measurements. Moreover, researchers were blinded for questionnaire data during the CPET and for test outcomes at T_0 during the CPET at T_1 . CPET outcomes were

analysed by a trained researcher. Oxygen uptake (VO_2) and RER values were averaged over 30 seconds at peak exercise. The VO_2 at the anaerobic threshold ($\text{VO}_{2\text{AT}}$) was determined as described elsewhere.³⁰

Questionnaires

On the same day, shortly before the CPET subjects were asked to complete the DASI, VSAQ, and FitMáx as self-reported questionnaires. The DASI consists of twelve dichotomous questions, of which weighted scores are used in an algorithm to estimate the $\text{VO}_{2\text{peak}}$.¹¹ The VSAQ is a single-answer 13-point scale describing activities of increasing intensity. The VSAQ score and age were used to estimate $\text{VO}_{2\text{peak}}$, according to guidelines of the questionnaire.¹² The FitMáx consists of 3 single-answer, multiple-choice questions assessing the maximum capacity of walking, stair climbing, and cycling on a 14-, 11- and 12-point scale, respectively. Based on the weighted score of the FitMáx combined with sex, age (in whole years), and BMI, $\text{VO}_{2\text{peak}}$ was estimated.¹⁷ The ability of the current study population to complete the FitMáx was assessed using 3 additional questions on a scale of 1–10 for the questions about walking, stair climbing, and cycling capacity separately, in which 1 indicates “I cannot estimate properly” and 10 indicates “I can estimate properly”.

Statistical analysis

A sample size estimation was performed using PASS 2008³¹, in which a sample size of $n=55$ was determined to achieve a two-way 95% confidence interval (CI) with an expected correlation of $r=0.60$ ($0.40 ; 0.75$). This is in line with the minimum of 50 participants as recommended in the COSMIN guidelines.²⁵ Statistical analyses were performed using SPSS version 23.0.³² Continuous variables were checked for normality using histograms and Q-Q plots. Continuous variables are presented as mean $\pm$ standard deviation (SD) in case of normal distribution or as median and interquartile range otherwise. Categorical variables are expressed as frequencies with percentages. Mean changes in outcomes between T_0 and T_1 were reported with 95% CI. When the 95% CI did not include zero, the mean change was considered statistically significant. Criterion validity and responsiveness were determined using ICC (two-way random absolute agreement), with corresponding 95% CI and standard error of the estimate (SEE). Criterion validity of the FitMáx, DASI, and VSAQ was evaluated for all participants at

T_0 , by quantifying the agreement between CPET- VO_2 peak and VO_2 peak estimated using the questionnaires (questionnaire- VO_2 peak). Furthermore, Bland-Altman analysis was conducted with calculation of bias and 95% LoA to assess the agreement between CPET- VO_2 peak and questionnaire- VO_2 peak and to determine whether mean differences between both values, are dependent on the size of the CPET- VO_2 peak. Proportional bias was assessed using linear regression between the means and the differences of CPET- VO_2 peak and questionnaire- VO_2 peak. P-values of <0.05 were considered statistically significant. In case of proportional bias, the ratio of questionnaire- VO_2 peak to CPET- VO_2 peak was calculated for each subject and plotted to the average of the two values with corresponding 95% LoA, as suggested by Bland and Altman.³³ To evaluate the responsiveness of the FitMáx, DASl, and VSAQ, the ICC and SEE were calculated between the absolute change in CPET- VO_2 peak (Δ CPET- VO_2 peak) and questionnaire VO_2 peak (Δ questionnaire- VO_2 peak) between T_0 and T_1 , for participants who completed both exercise tests. As a secondary analysis, the FitMáx- VO_2 peak without cycling was included for analysis as well, since it was expected that not all participants cycle regularly (on a regular bicycle without electronic support).

If the responsiveness to estimate Δ CPET- VO_2 peak was insufficient ($ICC < 0.5$), ROC-curves were plotted between the dichotomized Δ CPET- VO_2 peak (improvement vs no improvement) and the Δ questionnaire- VO_2 peak to assess whether the questionnaires at least were able to detect improvement in CPET- VO_2 peak.¹⁹⁻²¹ The minimal detectable change for improvement in CPET- VO_2 peak was defined as a relative increase of $\geq 6\%$.³⁴ The AUC of the ROC-curve with corresponding 95% CI was calculated to evaluate the ability of the questionnaires to detect a true improvement in CPET- VO_2 peak of $\geq 6\%$ over time. Since both sensitivity and specificity were considered equally important, the value at which the product of both is maximised was chosen as the optimal cut-off value to indicate an improvement in CPET- VO_2 peak.³⁵ Sensitivity, specificity, and predictive values (%) were calculated for the cut-off values of the questionnaires.

Results

Participants

Of the 84 patients who were eligible to participate in the study, 70 participants (83%) were included for analysis (15 men and 55 women). Twelve participants (17%) were lost to follow-up, because they did not complete any of the questionnaires and/or the CPET at T₁, for several reasons. Outcome measures at T₁ were available for 58 participants (83%) (Figure 6.1). Mean age at T₀ was 53.2 ± 12.8 years and breast cancer was the most common diagnosis (39%). Surgery, chemotherapy, and radiotherapy were the most commonly received treatments and approximately half of the participants were still receiving medical treatment during the study. Three of them (4%) were still receiving chemotherapy (Table 6.1).

Table 6.1. Patient characteristics at baseline (T₀).

	Participants who completed CPET and questionnaires at T ₀ (n=70)	Participants who completed CPET and questionnaires at T ₀ and T ₁ (n=58)
Sex		
Male	15 (21%)	9 (16%)
Female	55 (79%)	49 (85%)
Age (years)	53.2 (± 12.8)	54.1 (± 11.6)
Body Mass Index (kg/m ²)	27.6 (± 5.6)	27.5 (± 5.5)
Cancer type		
Breast cancer	27 (39%)	25 (43%)
Hematologic cancer	12 (17%)	7 (12%)
Cervix carcinoma	6 (9%)	4 (7%)
Lung cancer	5 (7%)	4 (7%)
Melanoma	4 (6%)	3 (5%)
Other	16 (23%)	15 (26%)
Metastasis		
No metastasis	37 (53%)	31 (53%)
Lymphatic metastasis	23 (33%)	19 (33%)
Bone metastasis	4 (6%)	3 (5%)
Other	6 (9%)	5 (9%)
Treatment		
Chemotherapy	49 (70%)	41 (71%)
Surgery	42 (60%)	39 (67%)
Radiotherapy	36 (51%)	31 (53%)
Hormone therapy	19 (27%)	18 (31%)
Immunotherapy	20 (29%)	15 (26%)
Stem cell transplantation	6 (9%)	5 (9%)
Treatment completed		
Yes	34 (49%)	28 (48%)
No	36 (51%)	30 (52%)

Results are displayed as n (%) or mean (± SD). kg/m²= kilograms per square meter; n = number of subjects.

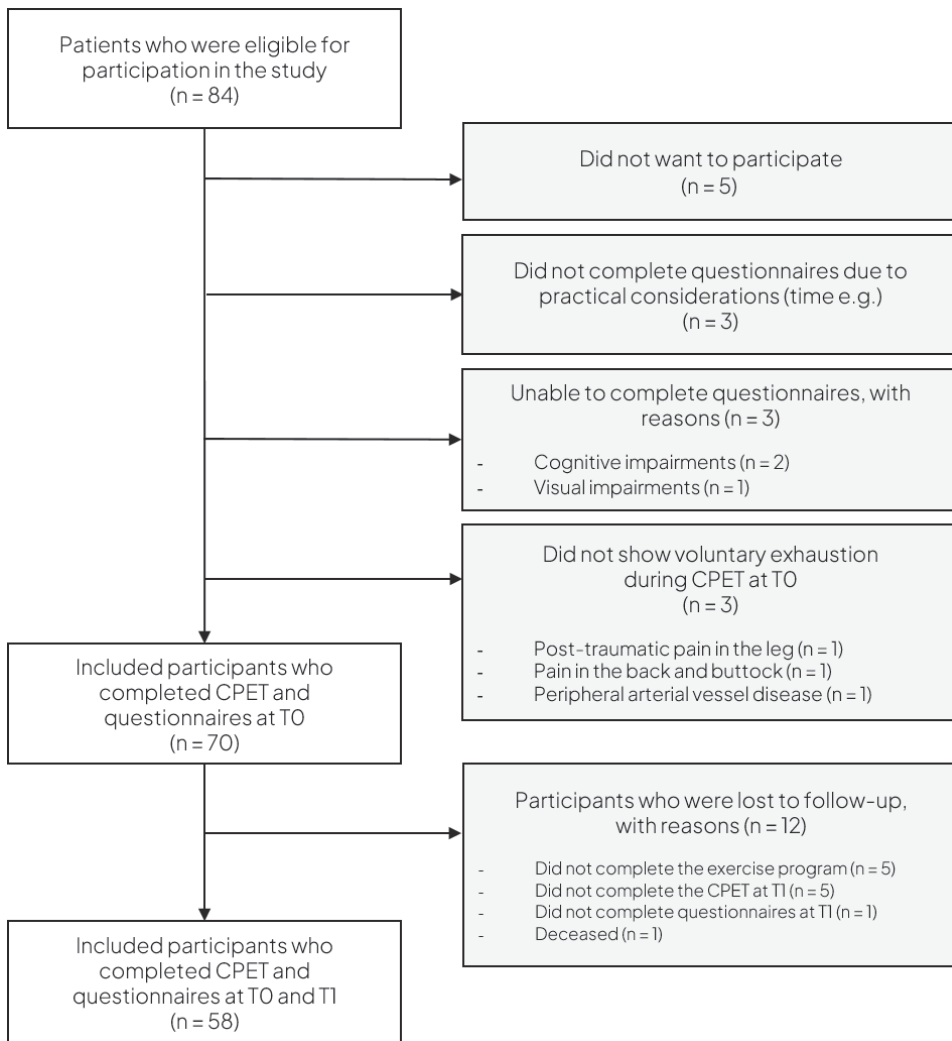


Figure 6.1. Participant inclusion flowchart. CPET = cardiopulmonary exercise test.

CPET and questionnaire results

Mean CPET- VO_2 peak at T_0 was 18.9 ± 5.9 mL/kg/min, which is $62 \pm 19\%$ of the reference value for healthy Dutch persons of the same age and sex.³⁶ Mean time between T_0 - T_1 was 94 ± 16 days. All included participants showed maximal voluntary exhaustion during CPET. At T_0 , $n=62$ participants (89%) met at least one of the objective criteria for true maximal effort during CPET

and at T₁, n=46 (79%). For RER_{peak} and heart rate at peak exercise (HR_{peak}), no significant differences were seen between T₀ and T₁. Participants who completed the tests and questionnaires at both T₀ and T₁ showed a significant mean improvement of 1.6 mL/kg/min (95% CI 1.0 ; 2.3) or 8% on CPET-VO_{2peak} after completion of the exercise program. Thirty-four participants (59%) showed a relative increase of ≥6% in CPET-VO_{2peak} which we considered as a true improvement in aerobic capacity.³⁴ Body weight, VO_{2AT} during CPET, FitMáx-VO_{2peak}, DASI-VO_{2peak} and VSAQ-VO_{2peak} increased significantly as well (Table 6.2). Most missing values were observed for DASI-VO_{2peak}. Because some participants did not fill out the FitMáx question about cycling, a sub-analysis was performed without the maximum cycling capacity.¹⁷ CPET results and questionnaire-VO_{2peak} are presented in Table 6.2 for all participants at T₀ (n=70) and for the participants who completed CPET and the questionnaires at both T₀ and T₁ (n=58), with corresponding change scores. The participants' ability to complete the FitMáx on a scale from 1-10 is reported as well.

Criterion validity

An ICC of 0.69 (95% CI 0.18 ; 0.86) was found for the agreement between CPET-VO_{2peak} and FitMáx-VO_{2peak} at T₀. When the question about maximum cycling capacity was not included, the ICC was 0.62 (95% CI 0.01 ; 0.84) for the agreement with CPET-VO_{2peak}. Less agreement was found between CPET-VO_{2peak} and VSAQ-VO_{2peak} (ICC=0.53) and CPET-VO_{2peak} and DASI-VO_{2peak} (ICC=0.37) (Table 6.3). The agreement between questionnaire-VO_{2peak} and CPET-VO_{2peak} is displayed visually in Figure 6.2A-D. Bland-Altman plots showed proportional bias for the agreement between CPET-VO_{2peak} and FitMáx-VO_{2peak}, FitMáx-VO_{2peak} without cycling, and VSAQ-VO_{2peak} (p<0.05). For this reason, bias and 95% LoA were reported as ratios.³³ The mean ratio of FitMáx-VO_{2peak}/CPET-VO_{2peak} was 1.21 (95% LoA 0.80 ; 1.62), which means the FitMáx overestimated CPET-VO_{2peak} with 21% on average. The mean ratio bias was 1.28 (95% LoA 0.81 ; 1.75) for FitMáx-VO_{2peak} without cycling, 1.06 (95% LoA 0.33 ; 1.79) for VSAQ-VO_{2peak} and 1.26 (95% LoA 0.55-1.97) for DASI-VO_{2peak}. Bland-Altman plots show wider 95% LoA for VSAQ and DASI when compared to FitMáx. The plots for FitMáx-VO_{2peak} with and without maximum cycling capacity look similar, but the results are shifted more towards a ratio above 1 for the FitMáx-VO_{2peak} without maximum cycling capacity. SEE for the agreement between CPET-VO_{2peak} and FitMáx-

VO₂peak, FitMáx-VO₂peak without cycling, VSAQ-VO₂peak and DASl-VO₂peak was 3.28 mL/kg/min, 3.31 mL/kg/min, 4.95 mL/kg/min and 5.46 mL/kg/min, respectively (Figure 6.3A-D; Table 6.3).

Table 6.2. CPET and questionnaire results.

	Participants who completed CPET and questionnaires at T ₀ (n=70) ^a	Participants who completed CPET and questionnaires at T ₀ and T ₁ (n=58) ^b		
		T ₀	T ₁	ΔT ₀ en T ₁
Anthropometric data				
Body weight (kg)	77.4 ± 15.5	76.5 ± 15.2	77.4 ± 15.7	0.9 (0.2–1.7)*
CPET data				
CPET-VO ₂ peak (mL/kg/min)	18.9 ± 5.9	18.5 ± 5.4	20.1 ± 5.9	1.6 (1.0 ; 2.3)*
% of the reference VO ₂ peak ^c	62 ± 19	62 ± 18	67 ± 19	6 (4 ; 7)
HRpeak (beats/min)	147 ± 22	147 ± 21	148 ± 20	1 (–3 ; 5)
RERpeak (VCO ₂ /VO ₂)	1.16 ± 0.09	1.15 ± 0.09	1.16 ± 0.09	0.01 (–0.01 ; 0.03)
VO _{2AT} (mL/kg/min)	11.6 ± 3.2	11.4 ± 2.9	12.8 ± 3.1	1.3 (0.7 ; 1.9)*
Δ Time CPET T ₀ –T ₁ (days)	–	–	–	94 (89 ; 98)*
Questionnaire data				
FitMáx- VO ₂ peak (mL/kg/min)	23.2 ± 7.7	22.7 ± 6.1	24.7 ± 6.6	1.9 (0.6 ; 3.3)*
FitMáx- VO ₂ peak without cycling (mL/kg/min)	23.8 ± 7.5	23.5 ± 6.6	25.3 ± 6.9	1.8 (0.5 ; 3.2)*
VSAQ- VO ₂ peak (mL/kg/min)	19.4 ± 7.4	18.0 ± 6.1	21.3 ± 8.4	3.2 (1.4 ; 5.1)*
DASI-VO ₂ peak (mL/kg/min)	22.9 ± 6.0	22.2 ± 6.1	25.3 ± 5.4	3.1 (1.4 ; 4.8)*
Ability to estimate FitMáx scores 1–10				
Walking score estimate	8 (7–9)	8 (7–9)	8 (7–10)	–
Stairclimbing score estimate	8 (6–9)	8 (6–8)	8 (7–9)	–
Cycling score estimate	5 (3–8)	5 (3–7)	6 (4–8)	–

Means ±SDs are presented for subjects who completed the CPET and questionnaires at T₀. For subjects who completed CPET and questionnaires at T₀ and T₁, means ±SDs are presented for both time points with the mean difference and corresponding 95%-CI. *Statistically significant. The ability to estimate the maximum capacity of walking, cycling and stairclimbing (1–10) is reported as median (interquartile range). ^a Missing values for subjects who performed CPET and filled in questionnaires at T₀ (n=70): VO_{2AT} n=1, FitMáx n=5, FitMáx without cycling n=1, DASl n=9, walking score estimate n=2, stairclimbing score estimate n=2, cycling score estimate n=3. ^b Missing values for subjects who completed CPET and questionnaires at T₀ and T₁ (n=58): VO_{2AT} n=1, FitMáx n=7, FitMáx without cycling n=2, DASl n=13, walking score estimate n=1, stairclimbing score estimate n=1, cycling score estimate n=1. ^c Mean VO₂peak calculated by prediction model for VO₂peak of the LowLands Fitness Registry for the general Dutch population was 31.0 ± 5.8 mL/kg/min for this population at T₀.³⁶ CPET=cardiopulmonary exercise test; DASl=duke activity status index; HRpeak= heart rate at peak exercise; kg=kilograms; mL=millilitres; mi= minute; n=number of subjects; RERpeak=peak respiratory exchange ratio; VO_{2AT}=oxygen uptake at the anaerobic threshold; VO₂peak=peak oxygen uptake; VSAQ=veterans specific activity questionnaire.

Table 6.3. Agreement between CPET-VO_{2peak} and questionnaire-VO_{2peak} at T₀.

Variable	n	ICC	95% CI	SEE	Mean ratio bias	Ratio lower 95% LoA	Ratio upper 95% LoA
CPET-VO _{2peak}	70	n/a	n/a	n/a	n/a	n/a	n/a
FitMáx-VO _{2peak}	65	0.69	0.18 ; 0.86*	3.28	1.21	0.80	1.62
FitMáx-VO _{2peak} without cycling	69	0.62	0.01 ; 0.84*	3.31	1.28	0.81	1.75
VSAQ-VO _{2peak}	70	0.53	0.34 ; 0.68*	4.95	1.06	0.33	1.79
DASI-VO _{2peak}	61	0.37	0.10 ; 0.59*	5.46	1.26	0.55	1.97

Number of subjects per questionnaire (n), ICC with corresponding 95% CI, SEE and mean ratio bias with 95% LoA are reported for the relation between CPET-VO_{2peak} and questionnaire-VO_{2peak} at T₀. *Statistically significant. CPET=cardiopulmonary exercise test; DASI=duke activity status index; ICC=intraclass correlation; n=number of subjects; n/a=not applicable; SEE=standard error of the estimate; VO_{2peak}=peak oxygen uptake; VSAQ=veterans specific activity questionnaire; 95% CI= 95% confidence interval; 95% LoA=95% limits of agreement.

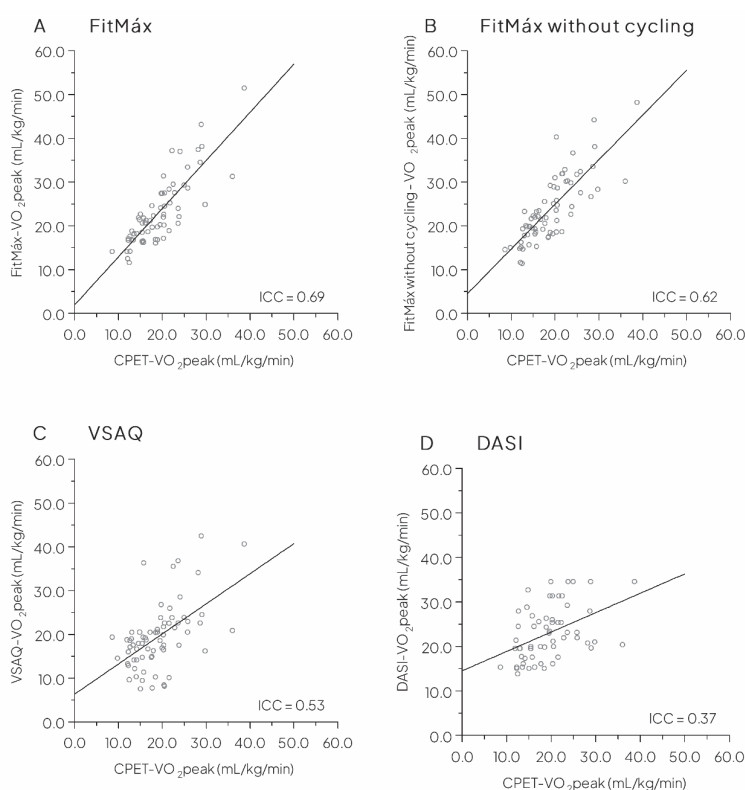


Figure 6.2A-D. Criterion validity with identity line for relation between questionnaire-VO_{2peak} and CPET-VO_{2peak} at T₀. A) FitMáx-VO_{2peak} compared with CPET-VO_{2peak} B) FitMáx-VO_{2peak} without cycling compared with CPET-VO_{2peak} C) VSAQ-VO_{2peak} compared with CPET-VO_{2peak} D) DASI-VO_{2peak} compared with CPET-VO_{2peak}. CPET=cardiopulmonary exercise test; DASI=duke activity status index; ICC=intraclass correlation coefficient; kg=kilograms; mL=millilitres; min=minute; VO_{2peak}=peak oxygen uptake; VSAQ=veterans specific activity questionnaire.

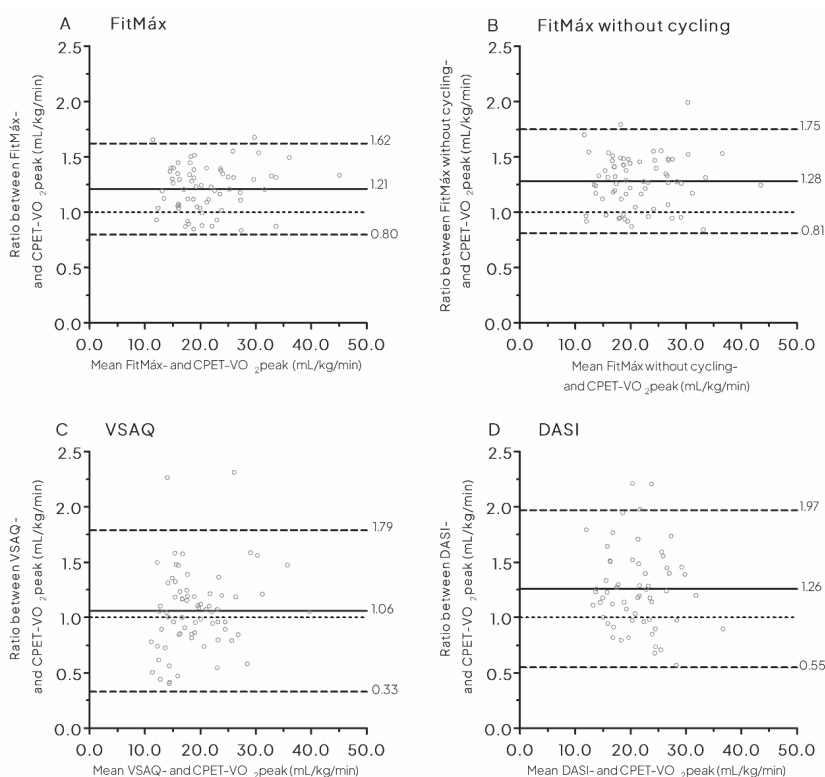


Figure 6.3A-D. Bland-Altman plots for the agreement between questionnaire- VO_2peak and CPET- VO_2peak at T_0 . The dashed lines represent the 95% LoA, from -1.96 SD to $+1.96$ SD. The solid line represents bias and the dotted line represents the zero bias line. A) FitMáx- VO_2peak compared with CPET- VO_2peak B) FitMáx- VO_2peak without cycling compared with CPET- VO_2peak C) VSAQ- VO_2peak compared with CPET- VO_2peak D) DASI- VO_2peak compared with CPET- VO_2peak . CPET=cardiopulmonary exercise test; DASI= duke activity status index; kg=kilograms; mL=millilitres; min=minute; VO_2peak =peak oxygen uptake; VSAQ=veterans specific activity questionnaire.

Responsiveness

An ICC of 0.43 (95% CI 0.18 ; 0.63) was found for the agreement between individual $\Delta\text{FitMáx-VO}_2\text{peak}$ and $\Delta\text{CPET-VO}_2\text{peak}$ from T_0 to T_1 . The ICC agreement between $\Delta\text{FitMáx-VO}_2\text{peak}$ without the question about maximum cycling capacity and $\Delta\text{CPET-VO}_2\text{peak}$ was 0.27 (95% CI 0.00 ; 0.49). A lower ICC was found for the agreement between $\Delta\text{CPET-VO}_2\text{peak}$ and $\Delta\text{VSAQ-VO}_2\text{peak}$ (ICC=0.19, 95% CI -0.06 ; 0.42) and the agreement between $\Delta\text{CPET-VO}_2\text{peak}$ and $\Delta\text{DASI-VO}_2\text{peak}$ (ICC = 0.18, 95% CI -0.10 ;

0.44) (Table 6.4; Figure 6.4A-D). Since the responsiveness to estimate Δ CPET-VO₂peak was insufficient for all questionnaires, ROC analyses were performed to determine whether the questionnaires are able to detect a true improvement in CPET-VO₂peak ($\geq 6\%$) with a corresponding optimal cut-off value.³⁴ An area under the curve (AUC) of 0.77 (95% CI 0.63 ; 0.91) was found for FitMáx-VO₂peak, while the FitMáx without maximum cycling capacity showed an AUC of 0.72 (95% CI 0.59 ; 0.86). The ROC-curve for VSAQ-VO₂peak and DASI-VO₂peak showed an AUC of 0.66 (95% CI 0.52 ; 0.80) and 0.64 (95% CI 0.48 ; 0.81), respectively (Table 6.4; Figure 6.5). The maximum product of sensitivity and specificity was found at $\Delta 1.0$ mL/kg/min, for FitMáx-VO₂peak and $\Delta 1.8$ mL/kg/min for FitMáx-VO₂peak without maximum cycling capacity. These values were therefore chosen as the optimal cutoff values to discriminate between improvement and no improvement in CPET-VO₂peak. The optimal cutoff value for VSAQ-VO₂peak was $\Delta 3.4$ mL/kg/min and $\Delta 2.7$ mL/kg/min for DASI-VO₂peak. Using the cutoff value for FitMáx-VO₂peak, resulted in a sensitivity of 71% a specificity of 75%, a positive predictive value (PPV) of 81% and a negative predictive value (NPV) of 63%. Sensitivity, specificity, PPV and NPV for the other questionnaires are presented in Table 6.4.

Table 6.4. Agreement between CPET-VO₂peak and Questionnaire-VO₂peak for changes (Δ) from T₀ to T₁.

Variable	n	ICC	95% CI	SEE	AUC	95% CI	Cutoff value	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Δ CPET-VO ₂ peak	58	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Δ FitMáx-VO ₂ peak	51	0.43	0.18;0.63*	2.07	0.77	0.63;0.91	1.0	71	75	81	63
Δ FitMáx-VO ₂ peak without cycling	56	0.27	0.00;0.49*	2.23	0.72	0.59;0.86	1.8	61	78	80	58
Δ VSAQ-VO ₂ peak	58	0.19	-0.06;0.42	2.25	0.66	0.52;0.80	3.4 ^o	62	58	68	52
Δ DASI-VO ₂ peak	45	0.18	-0.10;0.44	2.40	0.64	0.48;0.81	2.7	62	63	70	55

Number of subjects per variable (n) and ICC with corresponding 95% CI are reported for the relation between Δ CPET-VO₂peak and Δ questionnaire-VO₂peak from T₀ to T₁* Statistically significant. ^oThe cut-off value for VSAQ-VO₂peak is also the smallest improvement (which is ~equal to 1.0 MET) that could be measured with VSAQ.¹² AUC=area under the curve; CPET=cardiopulmonary exercise test; DASI=duke activity status index; ICC=intraclass correlation; n=number of subjects; n/a=not applicable; NPV=negative predictive value; PPV=positive predictive value; SEE=standard error of the estimate; Spec=specificity; Sens=sensitivity; VO₂peak=peak oxygen uptake; VSAQ=veterans specific activity questionnaire; 95% CI=95% confidence interval.

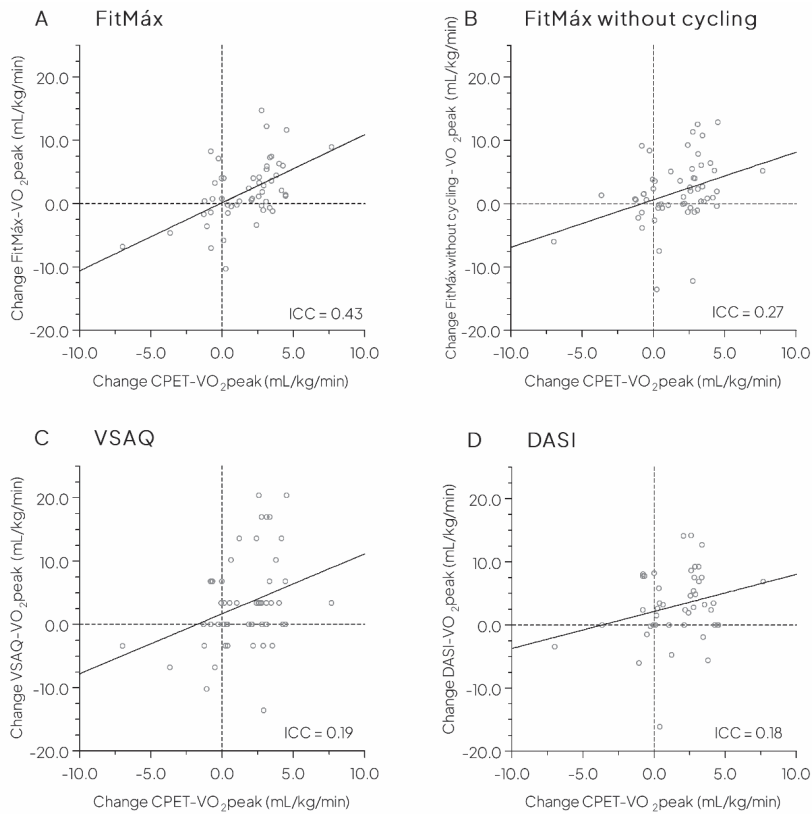


Figure 6.4A-D. Scatterplots for the relation between changes (Δ) in questionnaire- VO_2peak and CPET- VO_2peak from T_0 - T_1 . A) $\Delta\text{FitMáx-VO}_2\text{peak}$ compared with $\Delta\text{CPET-VO}_2\text{peak}$ B) $\Delta\text{FitMáx-VO}_2\text{peak}$ without cycling compared with $\Delta\text{CPET-VO}_2\text{peak}$ C) $\Delta\text{VSAQ-VO}_2\text{peak}$ compared with $\Delta\text{CPET-VO}_2\text{peak}$ D) $\Delta\text{DASI-VO}_2\text{peak}$ compared with $\Delta\text{CPET-VO}_2\text{peak}$. CPET= cardiopulmonary exercise test; DASI=duke activity status index; ICC=intraclass correlation coefficient; kg=kilograms; mL=milliliters; min=minute; VO_2peak =peak oxygen uptake; VSAQ=veterans specific activity questionnaire.

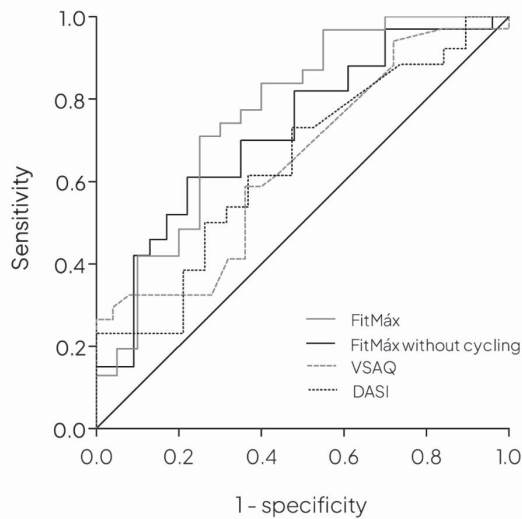


Figure 6.5. ROC-curves for the ability of questionnaires to detect a true improvement in CPET-VO₂peak. DASI=duke activity status index; ROC-curve=receiver operating characteristics curve; VSAQ=veterans specific activity questionnaire.

Discussion

In this study among cancer survivors who participated in a 10-week exercise program, we evaluated the criterion validity of 3 questionnaire and found a moderate agreement between FitMáx-VO₂peak and CPET-VO₂peak. Agreement between CPET-VO₂peak and VSAQ-VO₂peak was moderate as well, but lower compared to FitMáx-VO₂peak, while the DASI-VO₂peak showed poor agreement. This implies that the criterion validity of the DASI to evaluate aerobic capacity was insufficient. The criterion validity of the FitMáx and the VSAQ to estimate aerobic capacity is acceptable on group level, but limited to estimate CPET-VO₂peak in individuals.¹⁹

Initial Bland-Altman analysis showed proportional bias, indicating that mean differences between questionnaire-VO₂peak and CPET-VO₂peak with corresponding 95% LoA, are dependent on the size of the CPET-VO₂peak values. This is not surprising, since higher measurement errors are expected for higher values of CPET-VO₂peak.³⁴ For the latter reason, Bland-Altman analyses were performed using ratios instead of differences between questionnaire-VO₂peak and CPET-VO₂peak, which showed an overestimation of CPET-VO₂peak for all questionnaires.³³ Mean ratio bias

for FitMáx-VO₂peak (+21%) was smaller compared to DASI-VO₂peak (+26%), but larger compared to VSAQ-VO₂peak (+6%). However, 95% LoA for VSAQ-VO₂peak were wider compared to those for FitMáx-VO₂peak. This could be explained by larger measurement errors for VSAQ-VO₂peak in both directions, while FitMáx and DASI overestimated CPET-VO₂peak in most cases.

The moderate agreement found between questionnaire-VO₂peak and CPET-VO₂peak is in line with previous research, which showed discrepancies between patient-reported functional capacity and measured VO₂peak.^{13,37} A recent study of Meijer et al., reported higher values for the agreement between CPET-VO₂peak and FitMáx-VO₂peak, DASI-VO₂peak, and VSAQ-VO₂peak. On the other hand, SEE for FitMáx-VO₂peak and VSAQ-VO₂peak were smaller in the current study, compared to the previous study, indicating more accurate predictions of CPET-VO₂peak.¹⁷ It was not possible to compare Bland-Altman results with previous studies, because ratios were used instead of absolute values in the current study. In the original studies about the development of DASI and VSAQ, higher correlation coefficients between estimated and measured aerobic capacity were found, but the populations and research methods differed substantially from our study and both studies were performed more than 25 years ago.^{11,12} Low ICC values for the agreement between questionnaire-VO₂peak and CPET-VO₂peak at T₀ in the current study, could be explained by the small range in VO₂peak values.³⁸ The current study population had a relatively low aerobic capacity (62% of predicted) and the population was more homogeneous compared to the original FitMáx study.¹⁷ The fact that participants in the current study reached lower fitness levels compared to participants in the original FitMáx study (in which the questionnaire and its prediction model were developed), may have influenced the performance of the questionnaire as well. It can be expected that estimating physical abilities is easier when someone is fitter and reaches higher physical activity levels in daily life or even in sports. For patients who are mainly sedentary, it might be more difficult to estimate their physical abilities. Moreover, it could be questioned whether the question about cycling of the FitMáx is appropriate for the current study population. The area of the MUMC+ is hilly, making it difficult for elderly to cycle on a regular bike, especially after receiving cancer treatment. When patients did not cycle regularly or cycled on an electronic bike, it may have been hard for them to answer the FitMáx

question about maximum cycling capacity. This is in line with the fact that participants rated their ability to complete the FitMáx question about cycling with a median of 5 at T₀ and 6 at T₁, which is lower compared to the other two questions about walking and stair climbing.

All 3 questionnaires showed poor responsiveness to measure Δ CPET-VO₂peak in the current study population. This could be explained by the increased measurement error that comes along with repeated testing and by the little variability in data as well.^{20,21,38} However, ROC analysis showed that FitMáx-VO₂peak was sufficiently responsive to detect a true improvement in CPET-VO₂peak (AUC 0.77) when using the optimal cut-off value of 1.0 mL/kg/min.³⁴ This was also the case for the FitMáx-VO₂peak without the question about maximum cycling capacity (AUC 0.72 with a cut-off value of 1.8 mL/kg/min). The AUC for DASI-VO₂peak (0.64) and VSAQ-VO₂peak (0.66) were insufficient to detect improvement, and therefore it is not recommended to use these questionnaires to monitor changes in aerobic capacity.

Compared to a previous study in which a mean change of 2.0 ± 2.3 mL/kg/min was found after a 10-week exercise program as part of multidisciplinary oncology rehabilitation in MUMC+, larger improvements in VO₂peak were expected.²³ This could be explained by the fact that the training stimulus in the current study was not given as intended, due to COVID-19. Because of this pandemic, patients were allowed to train only once a week instead of twice, and exercise training took place in smaller groups of four instead of eight patients. In order to avoid a long waiting list, the training frequency was reduced. The smaller improvement may have led to less variability in Δ VO₂peak from T₀ to T₁, which could explain low ICC values for responsiveness. Results for responsiveness could not be compared with literature, because no previous studies were conducted on this matter.

Comparing the results for the different questionnaires, we can conclude that values for criterion validity and responsiveness of the FitMáx-VO₂peak are better compared to VSAQ-VO₂peak and DASI-VO₂peak, in cancer survivors participating in an exercise program. FitMáx-VO₂peak was less accurate without the question for maximum cycling capacity, yet superior to the DASI and VSAQ.

Strengths of the current study

This is the first study to investigate the responsiveness of self-reported questionnaires to estimate $\Delta\text{VO}_2\text{peak}$. The direct comparison of the criterion validity and responsiveness of 3 different self-reported questionnaires, with CPET- VO_2peak as criterion standard measure, was a strength of this study. Since both measurements and the exercise training were part of usual care, the current study results can easily be translated into daily care in oncology rehabilitation in the Netherlands. Besides, we included patients who did and did not complete medical treatment yet, resulting in a variation of $\Delta\text{CPET-VO}_2\text{peak}$ in both directions, which is ideal to study the responsiveness of a measurement.^{5,21} Another strength of the study was blinding of participants and researchers for test outcomes to avoid bias.

Limitations of the current study

A limitation was the fact that the DASI was often not completed. A possible explanation is the use of twelve dichotomous questions also including some activities which are difficult to recognize for the general Dutch population, such as playing basketball. In the absence of only one answer, the DASI- VO_2peak could not be calculated. This suggests that the usability of the DASI is limited in this population. The fact that true maximum effort (according to objective criteria) was not reached during all CPETs, could be seen as a limitation as well. However, these findings are in agreement with previous studies, which reported that maximal effort criteria are often not reached in cancer survivors.^{23,39} Besides, it can be expected that these participants are also unable to reach and estimate their maximum capacity of walking, stairclimbing, cycling, and other daily tasks, as described in the self-reported questionnaires. Since mean RER_{peak} and HR_{peak} were similar at T_0 and T_1 , it is not expected that the delivered effort affected the study results. Another limitation was the fact that the study population is quite specific (79% women and in general low fitness) so results may not be generalisable to other patients with cancer. Validity and responsiveness for male cancer survivors could differ from the current study results, especially because VO_2peak is sex-dependent. Also the cancer type and treatment may influence the relationship between questionnaire- VO_2peak and CPET- VO_2peak . For instance, breast surgery and breast radiation may cause limitations in certain activities mentioned in the DASI and VSAQ that include

the upper body (i.e. lifting weights). More research is needed in a population with a better distribution of sex, cancer type, treatment and more variation in level of aerobic capacity. Also, research on the responsiveness of PROMs to measure deterioration in VO_2peak would be of additional value, since the current study focused on improvement. Monitoring deterioration in VO_2peak would be useful during intensive cancer treatment, like chemotherapy. In this case, rehabilitation can be started as soon as deterioration in VO_2peak is noted. Besides, PROMs for estimating aerobic capacity could potentially be improved in the future, by using computerised adaptive test (CAT) methods. CAT methods enable PROMs to be adapted to individual patients while maintaining direct comparability of the scores.^{40,41} Based on the patient's previous answers, a computer program personalises the next questions, in order to obtain precise information in an efficient manner. A CAT version of the FitMáx, could personalise questions on physical fitness for patients with different diagnoses of cancer, different treatment modalities, and different fitness levels, which could potentially lead to more precise estimations of VO_2peak and better values of validity and responsiveness.

Clinical relevance

Results of the current study show that the FitMáx is sufficiently valid to estimate aerobic capacity on group level and could be used to detect improvement using a cutoff value of 1.0 mL/kg/min. The advantage of such a questionnaire is the possibility to monitor aerobic capacity over time with repeated assessments at a low cost. When choosing self-reported questionnaires to evaluate aerobic capacity in cancer survivors, it can be recommended to use FitMáx above the DASI and VSAQ, since this recently developed questionnaire showed better criterion validity and responsiveness. However, results should be interpreted with caution, since values for criterion validity and responsiveness were still suboptimal, and it should be kept in mind that the FitMáx overestimates with on average 21% in this population.²⁵ Moreover, CPET is also used to determine the underlying cause of exercise limitations and contra-indications for physical exercise.⁹ Therefore, FitMáx should not be considered as a full replacement for CPET, but rather an alternative tool to be used in clinical or research settings where exercise testing is not feasible or necessary. In cancer survivors with increased cardiovascular risks, such as pre-existing cardiovascular disease, treatment with cardiotoxic chemotherapy and left-sided chest radiation,

performing CPET should still be recommended.⁴² An online platform (www.fitmaxquestionnaire.com) was developed, to enable healthcare professionals and researchers in using the FitMáx. The online platform provides up-to-date information about the questionnaire and research projects. More information about the research group, hospital and FitMáx can be found on <https://www.mmc.nl/english/fitmax/>.

Conclusion

The population specific criterion validity and responsiveness of the self-reported FitMáx-VO₂peak are better compared to VSAQ-VO₂peak and DASI-VO₂peak, in cancer survivors who participated in an exercise program as part of multidisciplinary rehabilitation. The FitMáx is sufficiently valid to estimate CPET-VO₂peak in cancer survivors on group level, but overestimates with on average 21%. The responsiveness of the FitMáx to measure absolute changes in CPET-VO₂peak was poor, but the questionnaire is able to detect whether aerobic capacity improved when using a cutoff value of only 1.0 mL/kg/min. Therefore, the self-reported FitMáx can be used to estimate and monitor aerobic capacity in cancer survivors, but results should be interpreted with caution on absolute values since the agreement with the criterion standard is limited. Refinements of the questionnaire and the prediction model will be made in the future potentially leading to a further optimisation of the validity and responsiveness.

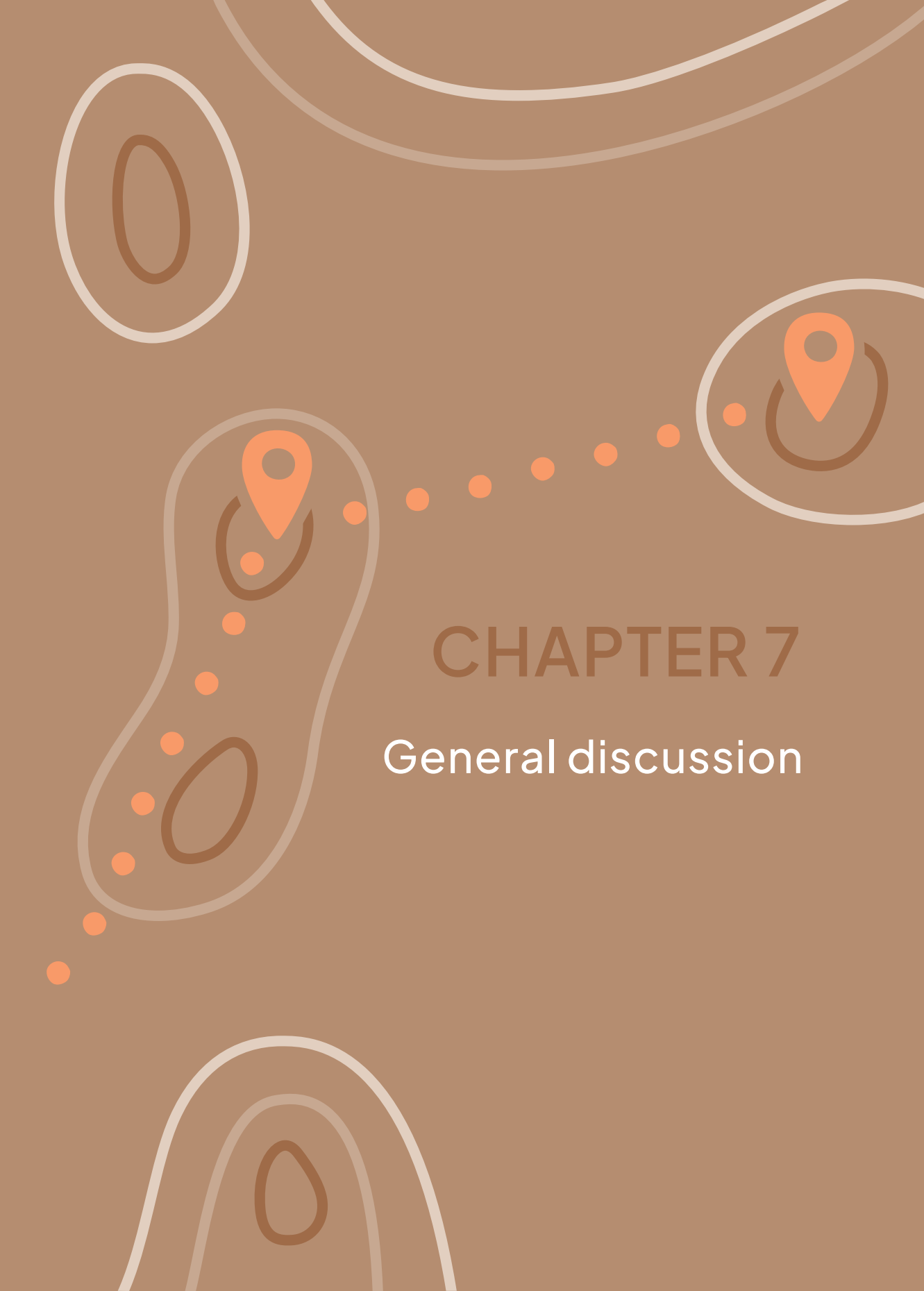
References

1. Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study. *Mayo Clin Proc* 2016;91(9):1183-1188.
2. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Fleenor BS, et al. The Association between the Change in Directly Measured Cardiorespiratory Fitness across Time and Mortality Risk. *Prog Cardiovasc Dis* 2019;62(2):157-162.
3. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
4. Yu AF, Flynn JR, Moskowitz CS, Scott JM, Oeffinger KC, Dang CT, et al. Long-term Cardiopulmonary Consequences of Treatment-Induced Cardiotoxicity in Survivors of ERBB2-Positive Breast Cancer. *JAMA Cardiol* 2020;5(3):309-317.
5. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al. Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol* 2018;36(22):2297-2305.
6. Campbell K, Winters-Stone K, Patel A, Gerber L, Matthews C, May A, et al. An Executive Summary of Reports From an International Multidisciplinary Roundtable on Exercise and Cancer: Evidence, Guidelines, and Implementation. *Rehabil Oncol* 2019;37:144-152.
7. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(2):211-277.
8. West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. *British Journal of Surgery* 2016;103(6):744-752.
9. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol* 2008;9(8):757-765.
10. Cancer rehabilitation. Nation-wide guideline. Utrecht: Comprehensive Cancer Centre of the Netherlands (IKNL); 2017 Report No.: Version 2.0. Available from <https://richtlijnendatabase.nl/>
11. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64(10):651-654.
12. Myers J, Do D, Herbert W, Ribisl P, Froelicher VF. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. *Am J Cardiol* 1994;73(8):591-596.
13. Li MH, Bolshinsky V, Ismail H, Ho KM, Heriot A, Riedel B. Comparison of Duke Activity Status Index with cardiopulmonary exercise testing in cancer patients. *J Anesth* 2018;32(4):576-584.
14. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990;13(8):555-565.
15. da Silva SC, Monteiro WD, Cunha FA, Myers J, Farinatti PT. Determination of Best Criteria to Determine Final and Initial Speeds within Ramp Exercise Testing Protocols. *Pulm Med* 2012;2012:542402.
16. Kojima S, Wang DH, Tokumori K, Sakano N, Yamasaki Y, Takemura Y, et al. Practicality of Veterans Specific Activity Questionnaire in evaluation of exercise capacity of community-dwelling Japanese elderly. *Environ Health Prev Med* 2006;11(6):313-320.
17. Meijer R, van Hooff M, Papen-Botterhuis NE, Molenaar CJL, Regis M, Timmers T, et al. Estimating VO(2peak) in 18-90 Year-Old Adults: Development and Validation of the FitMax®-Questionnaire. *Int J Gen Med* 2022;15:3727-3737.
18. de Vet HCW, Terwee CB, Mokkink LB, Knol DL. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press; 2011.

19. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016;15(2):155-163.
20. Hopkins WG. Measures of Reliability in Sports Medicine and Science. *Sports Medicine* 2000;30(1):1-15.
21. de Vet HC, Bouter LM, Bezemer PD, Beurskens AJ. Reproducibility and responsiveness of evaluative outcome measures. Theoretical considerations illustrated by an empirical example. *Int J Technol Assess Health Care* 2001;17(4):479-487.
22. Myers J, Bader D, Madhavan R, Froelicher V. Validation of a specific activity questionnaire to estimate exercise tolerance in patients referred for exercise testing. *American Heart Journal* 2001;142(6):1041-1046.
23. Weemaes ATR, Beelen M, Bongers BC, Weijenberg MP, Lenssen AF. Criterion Validity and Responsiveness of the Steep Ramp Test to Evaluate Aerobic Capacity in Survivors of Cancer Participating in a Supervised Exercise Rehabilitation Program. *Arch Phys Med Rehabil* 2021;102(11):2150-2156.
24. Rickham PP. Human Experimentation. Code Of Ethics Of The World Medical Association. Declaration Of Helsinki. *Br Med J* 1964;2(5402):177.
25. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010;19(4):539-549.
26. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122(2):191-225.
27. O'Connor FG. *ACSM's Sports Medicine: A Comprehensive Review*. Wolters Kluwer Health; 2012.
28. Wagner J, Niemeyer M, Infanger D, Hinrichs T, Streese L, Hanssen H, et al. New Data-based Cutoffs for Maximal Exercise Criteria across the Lifespan. *Med Sci Sports Exerc* 2020;52(9):1915-1923.
29. Brawner CA, Ehrman JK, Schairer JR, Cao JJ, Keteyian SJ. Predicting maximum heart rate among patients with coronary heart disease receiving beta-adrenergic blockade therapy. *Am Heart J* 2004;148(5):910-914.
30. Weemaes ATR, Weijenberg MP, Lenssen AF, Beelen M. Exercise training as part of multidisciplinary rehabilitation in cancer survivors: an observational study on changes in physical performance and patient-reported outcomes. *Support Care Cancer* 2022:1-12.
31. PASS 2008. Kaysville, Utah, USA: NCSS, LLC; 2008.
32. Corp. I. *IBM SPSS Statistics for Windows, Version 23.0*. 2015.
33. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8(2):135-160.
34. Keteyian SJ, Brawner CA, Ehrman JK, Ivanhoe R, Boehmer JP, Abraham WT. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise parameters: implications for clinical trials and clinical practice. *Chest* 2010;138(4):950-955.
35. Nahm FS. Receiver operating characteristic curve: overview and practical use for clinicians. *Korean J Anesthesiol* 2022;75(1):25-36.
36. van der Steeg GE, Takken T. Reference values for maximum oxygen uptake relative to body mass in Dutch/Flemish subjects aged 6-65 years: the LowLands Fitness Registry. *Eur J Appl Physiol* 2021;121(4):1189-1196.
37. Stokes JW, Wanderer JP, McEvoy MD. Significant discrepancies exist between clinician assessment and patient self-assessment of functional capacity by validated scoring tools during preoperative evaluation. *Perioper Med (Lond)* 2016;5:18.
38. Goodwin LD, Leech NL. Understanding Correlation: Factors That Affect the Size of r. *The Journal of Experimental Education* 2006;74(3):249-166.

39. Santa Mina D, Au D, Papadopoulos E, O'Neill M, Diniz C, Dolan L, et al. Aerobic capacity attainment and reasons for cardiopulmonary exercise test termination in people with cancer: a descriptive, retrospective analysis from a single laboratory. *Support Care Cancer* 2020;28(9):4285-4294.
40. Petersen MA, Groenvold M, Aaronson NK, Chie WC, Conroy T, Costantini A, et al. Development of computerized adaptive testing (CAT) for the EORTC QLQ-C30 physical functioning dimension. *Qual Life Res* 2011;20(4):479-490.
41. Petersen MA, Aaronson NK, Conroy T, Costantini A, Giesinger JM, Hammerlid E, et al. International validation of the EORTC CAT Core: a new adaptive instrument for measuring core quality of life domains in cancer. *Qual Life Res* 2020;29(5):1405-1417.
42. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;30(20):2530-2537.



The background is a solid brown color. It features several abstract, organic shapes in a lighter brown shade. A dotted path of small orange circles starts from the bottom left, moves upwards and to the right, and then curves to the right, ending near a location pin icon. There are also other location pin icons and small orange dots scattered within the organic shapes.

CHAPTER 7

General discussion

The number of people facing the complex health issues resulting from cancer and its treatment is increasing and adequate survivorship care to address these issues is needed.¹ Physical exercise rehabilitation is an important part of survivorship care. The benefits of physical activity (PA) and structured exercise directly after treatment are well-described in the literature, but it could be questioned if research results are translatable to cancer survivors with complex, interrelated physical and psychosocial complaints.² Furthermore, side effects of cancer and its treatment are often long-standing, which makes it necessary for healthcare providers and researchers to look beyond rehabilitation programs and even ‘outside the hospital walls’. A healthcare system like this would ask for the involvement of multiple survivorship care providers and practical considerations, like the use of approachable and affordable measurement tools.

The main aim of this thesis was to monitor changes in physical fitness (i.e. aerobic capacity and muscle strength) and patient-reported outcomes (i.e. health-related quality of life (HRQoL); fatigue; anxiety and depression) during a supervised exercise program as part of multidisciplinary oncology rehabilitation, optimise the transition to independent long-term PA maintenance, and assess the validity and responsiveness of different methods to monitor aerobic capacity. In this chapter, the main findings of the studies described in this thesis are discussed, methodological considerations are addressed and implications for practice and future research are provided.

Main findings

In **Chapter 2**, the findings of a usual-care evaluation of an exercise program as part of multidisciplinary rehabilitation at the Maastricht University Medical Centre (MUMC+) are described.³ This multidisciplinary program comprises a 10-week group-based, supervised exercise program, supplemented with one or more additional interventions aiming at improving mental health, chronic fatigue, work reintegration, and nutritional status. Results showed that cancer survivors show statistically significant improvements in physical fitness and patient-reported outcomes after completing the 10-week supervised exercise program. Improvement was clinically relevant for nearly all outcomes. Unfortunately and unexpectedly, the program was interrupted and later adapted with reduced training time and frequency due

to restrictions during the coronavirus-19 (COVID-19) pandemic. Reduction in training time and frequency during the COVID-19 pandemic resulted in smaller changes in most performance outcomes. However pre-post differences remained statistically significant. These findings implicate that a 'dose-response' relation exists between exercise volume and its effect on physical fitness, with a higher exercise volume leading to larger effects.

Findings of the randomised controlled trial (RCT) in **Chapter 3** indicated that a six-month remote coaching intervention provided after a supervised exercise oncology program as part of multidisciplinary rehabilitation was not effective to improve the maintenance of PA levels, physical fitness, and patient-reported outcomes. A between-group difference of 45 minutes of PA per week suggested that participants who received the remote coaching intervention maintained PA levels slightly better compared to participants who received no additional intervention, but this difference was not statistically significant. The ability to maintain PA levels after a supervised rehabilitation program varied considerably across participants and was not affected by a remote coaching intervention. While the majority of the participants in both groups were able to maintain or improve PA levels, 39% of the participants reached values of aerobic capacity that were still below the lower limit of normal.⁴

The phenomenological qualitative study in **Chapter 4**, suggested that determinants of PA maintenance following a supervised exercise program were related to the level of self-efficacy, prior and newly formed PA habits, the feeling of accountability for PA maintenance, the presence of and fear for physical complaints and the accessibility of exercise facilities.⁵ Interview findings indicated that remote coaching was generally acceptable to cancer survivors who completed a supervised exercise program. Participants felt that the coaching positively affected PA maintenance, but the added value differed between participants. Some participants would have preferred face-to-face appointments, while others found the remote nature convenient.

The second part of this thesis focused on the methodology of measuring aerobic capacity. In **Chapter 5**, we investigated the validity and responsiveness of the steep ramp test (SRT), which is a short and practical performance test on a cycle ergometer.⁶ Given the strong correlation ($r=0.86$) between outcomes of the SRT and the cardiopulmonary exercise

test (CPET), which is the criterion standard for measuring aerobic capacity, the SRT proved to be valid to estimate aerobic capacity in cancer survivors. The responsiveness to measure the absolute change in aerobic capacity, on the other hand, was moderate ($r=0.51$). Receiver operating characteristic analysis showed that the SRT was able to detect improvement in aerobic capacity (area under the curve (AUC)=0.74) when using a cutoff value of 0.26 watts per kg bodyweight.

In **Chapter 6**, the validity and responsiveness of three different self-reported questionnaires to evaluate aerobic capacity were assessed and compared: the widely used Duke Activity Status Index (DASI) and Veterans Specific Activity Questionnaire (VSAQ), and the newly developed FitMáx-questionnaire© (hereafter: FitMáx).⁷ The FitMáx was recently developed to estimate aerobic capacity based on the self-reported maximum capacity of walking, stair climbing, and cycling combined with demographic characteristics. Results showed that the agreement between aerobic capacity measured during CPET and estimated by the questionnaires was moderate for FitMáx (ICC=0.69) and VSAQ (ICC=0.53), and poor for DASI (ICC=0.36). All questionnaires showed to have poor responsiveness to monitor changes in aerobic capacity (ICC of 0.43, 0.19, and 0.18 for FitMáx, VSAQ, and DASI, respectively). However, the FitMáx was able to detect change (AUC=0.77) with an optimal cutoff value of 1.0 mL/kg/min, while the DASI (AUC=0.64) and VSAQ (AUC=0.66) were not. Values for validity and responsiveness were better for FitMáx compared to DASI and VSAQ.

Methodological considerations

Methodological strengths and limitations were already reported in the discussion sections of the previous chapters, but three important topics are discussed more in-depth, to put the results of this thesis into perspective.

Study designs

The use of different study designs was a strength of this thesis, however, the differences and potential shortcomings of these designs should be taken into consideration when interpreting the results. In **Chapter 2** we presented the results of a pragmatic observational study, which was performed in clinical daily care. All participants of the rehabilitation program were eligible

for inclusion in this study and no additional actions were required from the participants, besides the use of their usual care data. This resulted in a high inclusion rate of 94% and therefore the results are expected to be realistic and generalisable to daily practice. However, the lack of a randomised control group and therefore the role of the natural course of recovery should be kept in mind when interpreting the changes in outcomes observed.^{8,9} It would be of interest to compare the effectiveness of an exercise program as part of multidisciplinary oncology rehabilitation as described in the Dutch guidelines with an exercise program as a single intervention, but this is not feasible because the program is part of usual care and it would be unethical to withhold cancer survivors from receiving this care.

In **Chapter 3** we described the findings of an RCT, which is seen as the most suitable design for investigating the efficacy of interventions. Nevertheless, RCTs also have limitations as they are described to lack generalisability to the clinical setting, because of the often strict inclusion criteria.^{8,9} In this study, 34% of the patients screened for eligibility did not meet the inclusion criteria, and 27% of the eligible patients refused to participate in the study. We believe this may have been a fitter and more motivated selection of participants since they met the inclusion criteria, were willing to attend the supervised rehabilitation program in the first place, and consented to participate in the RCT afterwards. The null results for the effectiveness of remote coaching might be explained by the fact that participants in both intervention arms were already motivated for PA maintenance and part of them did not need an additional intervention to maintain PA. While all cancer survivors who completed the supervised exercise program were eligible to participate in this study, in a future RCT, it may be more relevant to include only patients in need of a follow-up intervention, to investigate the effectiveness of remote coaching. In order to make this possible, research is first required on the identification of these survivors in need.

Study population

As already mentioned in the previous paragraph, the characteristics of the study population presumably had an influence on the results of the different studies. As cancer survivors represent a very heterogeneous group, it is important to zoom in on the characteristics of our study population. Participants of all studies reported in this thesis were recruited from the

supervised exercise program as part of multidisciplinary oncology rehabilitation, which is usual care at the Maastricht UMC+. This program is aimed at patients with all types of cancer who are suffering from interrelated physical and/or psychosocial complaints and/or fatigue.¹⁰ Therefore the results of this thesis are probably not generalisable to cancer survivors with less complex care needs.

Besides, it is remarkable that the majority of the participants included in our studies were women diagnosed with breast cancer, while the program is aimed at all types of cancer. Given the high participation rate in the observational study, we can assume that this percentage reflects the proportion of survivors of breast cancer in the multidisciplinary oncology rehabilitation at the Maastricht UMC+. Breast cancer is the most common cancer among women in the Netherlands and in 2022, approximately a quarter of all new cancer diagnoses concerned breast cancer, pre-invasive breast cancer not even included.¹¹ In our study, however, almost 50% of the participants were diagnosed with breast cancer, which means that they were overrepresented and were referred relatively more often compared to other cancer types. Van Nuenen et al. performed a study on the implementation of a screening- and referral method for cancer survivorship in 23 Dutch hospitals and concluded that this method was implemented more often in breast cancer patients, compared to other cancer types. This was explained by the important role of specialist nurses as ‘navigators’ in the entire patient journey of patients with breast cancer, which was often not available for patients with other cancer types.¹² We could assume that in the Maastricht UMC+ as well, the close involvement of the breast cancer nurses has led to better signalling of impaired functioning and consequently more referrals to oncology rehabilitation. A bibliometric analysis of cancer rehabilitation research in the last decades showed that most studies were done on breast cancer. While we purposely chose to include survivors of all types of cancer, our results probably apply best to survivors of breast cancer.¹³ When comparing our study results to previous research in breast cancer patients, we found some similarities, but some differences as well. In accordance with our results presented in **Chapter 2**, Leclerc et al. found significant effects of multidisciplinary rehabilitation on physical fitness and HRQoL in breast cancer patients. However, the improvements in VO₂peak observed in their study were larger compared to our study. This could be explained by the fact that all patients were eligible to participate in their

study after receiving breast cancer surgery, regardless of their complaints and care needs, while only cancer survivors with interrelated complaints were included in our study.¹⁴ In accordance with our findings, persistent declines (i.e. 6 months to 3 years post-treatment) in aerobic capacity were described before in patients with breast cancer.¹⁴

COVID-19 pandemic

The global break-out of the COVID-19 pandemic has largely influenced the conduct and the results of this thesis. Between March 2020 and July 2020, all outpatient activities including the oncology rehabilitation had to be cancelled abruptly in the MUMC+. For this reason, my colleagues and I developed a home-based program with advice according to the PA guidelines of the World Health Organization: at least 150 minutes of moderate-to-vigorous PA weekly and muscle or –bone-strengthening exercise at least twice weekly.¹⁶ Videos were recorded and published online with bodyweight and resistance band resistance exercises for the largest muscle groups, with different intensity levels (<https://www.mumc.nl/patient-bezoeker/specialismen-afdelingen/fysiotherapie/oefeningen-voor-thuis>). We encouraged patients to monitor their PA activities and exercise progress, by filling in provided training schedules. In July 2020, national guidelines permitted the resumption of the rehabilitation program. However, because of social distancing policies, exercise training had to take place in smaller groups of four instead of eight patients. Training frequency was reduced to once a week, to avoid long waiting lists. Moreover, contact sports and swimming were not allowed, so this part of the exercise training could not be restarted. The limited accessibility of the onsite rehabilitation program led to a shift in focus towards patients' self-management to PA in their home environment, which we believe should be an important element of cancer survivorship in the future. All study results presented in this thesis have probably been affected by the COVID-19 pandemic.

For the observational study described in **Chapter 2**, the results were definitely affected, because the content, time, and frequency of the exercise program changed. The COVID-19 pandemic has also negatively influenced the statistical power of this study because data collection had to be interrupted, some participants had to be excluded because the exercise program and measurements were not completed and analyses had to be

performed in subgroups. However, the changes in the program have offered the opportunity to look at the influence of training adaptations.

It could be expected that the COVID-19 restrictions affected the number of PA minutes/week as measured in the RCT in **Chapter 3** but did probably not influence the effectiveness, since participants were randomised. The qualitative study described in **Chapter 4** showed that the inaccessibility of facilities during the COVID-19 pandemic negatively affected PA maintenance. Self-efficacy turned out to be an important feature, defining patients' ability to cope with events that affect their lives, which in this case was not only the cancer diagnosis but also the COVID-19 pandemic. Findings about determinants for PA maintenance and acceptability of remote coaching would probably have been different if not examined during the COVID-19 pandemic. We believe that our research on remote coaching in **Chapters 3 and 4** became even more relevant since the COVID-19 pandemic because we were forced to deliver healthcare remotely during the pandemic and experienced the opportunities and challenges of telehealth.

The sample size and thereby the statistical power of the analyses of the responsiveness of the SRT in **Chapter 5** have been affected since some participants could not complete the exercise program and follow-up measurements.

The reduced training time and frequency have probably also affected the results on the responsiveness of the self-reported questionnaires in **Chapter 6**, because smaller improvements in aerobic capacity were observed, which may have led to less variability in the data, resulting in lower ICC values.¹⁷ The use of self-reported questionnaires to assess aerobic capacity became also more meaningful since these questionnaires enable healthcare providers to assess aerobic capacity remotely. In conclusion, we could say that the COVID-19 pandemic has been a challenge, but also an opportunity for this PhD trajectory.

Implications for clinical practice

The Maastricht UMC+ has been recognised as a Comprehensive Cancer Centre (MCCC) by the Organisation of European Cancer Institutes and aims to *‘provide patient-oriented, multidisciplinary care for oncology patients and study ways to improve the outcome of oncological (pre-)care along the continuum of prevention, diagnostics, treatment, nursing and care, and rehabilitation/post-care with a strong focus on ‘survival with preservation of function’.*¹⁸ With the increased healthcare demand, changes in healthcare practice are required in the near future to ensure suitable care, which is accessible and affordable. Because of the increasing pressure on the Dutch healthcare system, the Integrated Healthcare Agreement (IZA) was formulated and published in 2022 as a call for action.¹⁹ The IZA aims to provide *“the right care and support, together with the patient, in the right place and with a focus on health instead of disease”*. Implications of the current thesis for clinical practice and future research will be discussed in the context of the missions of the MCCC and the IZA.

Integrating rehabilitation in the continuum of the cancer journey

While the term cancer survivorship is often associated with the period after curation, cancer survivorship care addresses physical and psychosocial issues spanning from cancer diagnosis until the end of life.²⁰ Decades ago, Mullan et al. identified three phases of cancer survivorship referring to them as seasons: the season of acute survivorship, concerning the diagnosis and treatment phase, the extended survivorship as a period of ‘watchful waiting’, and the season of permanent survivorship, regarding long-term remission.²¹ Years later, Miller et al. suggested adding a fourth season of transitional survivorship to the original model between the acute and extended survivorship phase, because the transition from active medical treatment to beyond is often perceived as more difficult than the treatment itself.²² Survivors often experience a decrease in medical, social, and financial support during this phase and are confronted with the challenge of transitioning from “surviving to thriving”.

The benefits of rehabilitation and the need for long-term PA promotion

The transitional phase is also the period during which oncology rehabilitation often takes place because it is the moment when complaints become apparent and are reported to healthcare providers. In **Chapter 2**, we described the benefits of exercise training as part of multidisciplinary oncology rehabilitation during the transitional phase of survivorship care. However, the transitional phase does not end after supervised rehabilitation and the transition from rehabilitation to lifelong adherence to PA guidelines can be difficult for patients because medical supervision is reduced. In **Chapter 3**, participants reached on average 73% of the normative values for aerobic capacity six months after completing supervised rehabilitation. Furthermore, 39% of all participants reached values that were below the lower limit of normal, determined as the lowest 3% of the population in which the normative values were established.⁴ Given the high pressure on the healthcare system, future research should further investigate the potential of providing follow-up interventions (partly) remotely and in collaboration with community-based initiatives. The findings of the qualitative study in **Chapter 4** implicate that remote coaching interventions are perceived as acceptable to cancer survivors, should be personalised, and should focus on improving self-efficacy and habit formation, to help cancer survivors overcome PA barriers like physical complaints and limited accessibility of PA facilities. We recommend adding these elements to supervised rehabilitation programs and shifting the focus from exercise training to encouraging self-management, to stimulate long-term PA maintenance. Adding face-to-face appointments to remote coaching interventions could potentially enlarge the perceived effectiveness. More research is needed on the development, effectiveness, and implementation of follow-up interventions to stimulate long-term outcomes beyond supervised oncology rehabilitation programs since the remote coaching intervention investigated in **Chapter 3** did not prove to be effective.

From reactive to proactive, the role of prehabilitation

In **Chapters 2, Chapter 5, and Chapter 6**, we observed that participants had low levels of aerobic capacity at the start of the rehabilitation program. While this thesis focused more on the period beyond active medical

treatment, we believe that survivorship care should be provided already before and during treatment, to limit deterioration in aerobic capacity and prevent functional complaints. The current model of survivorship care in the Netherlands is 'reactive', acting when patients already experience impairments but is slowly evolving to a 'proactive' model of care. Different frameworks to move towards proactive survivorship care are described in the literature, proposing integration of ongoing monitoring of functional outcomes, promotion of a healthy lifestyle, and adequate referral to survivorship care throughout the entire patient journey, from diagnosis to long-term follow-up.^{23,24} When rehabilitation takes place before scheduled treatment, this is referred to as 'prehabilitation'. Prehabilitation is gaining traction worldwide and early results indicate that it can be effective to improve functional outcomes, treatment effectiveness, post-treatment recovery and even to decrease healthcare expenditure and mortality rates.^{25,26} While the concept of prehabilitation was originally founded for patients awaiting surgery, prehabilitation can also be delivered before or during chemotherapy, radiation, and stem cell therapy.²⁷ According to the guidelines of the American Society of Clinical Oncology, combined aerobic and resistance exercise during active treatment with systemic therapy or radiotherapy should be recommended, because this is effective to improve physical fitness and patient-reported outcomes.²⁸ Resistance training in patients with prostate cancer receiving androgen deprivation has been shown to counteract adverse effects on body composition, muscle mass, muscle strength, and aerobic capacity.²⁹ Combined endurance and resistance training during chemotherapy was also proven to be effective to reduce hospitalization rates in patients with breast cancer³⁰ and to reduce symptom burden (e.g. pain, vomiting, and constipation), and improve chemotherapy completion rates in patients with breast- or colon cancer.³¹ Miller et al.³² proposed the chemotherapy infusion appointments as an opportunity for initiating the conversation about exercise or even starting with exercise during the chemotherapy infusion. Animal studies suggest that light exercise during the chemotherapy infusion may improve the chemotherapy drug uptake of the tumour, but clinical research is required to confirm this in humans.

It could be assumed that in some cases, rehabilitation after treatment could be shortened or even eliminated when patients have completed prehabilitation or rehabilitation during treatment because functional decline

is limited and patients already have the skills and knowledge to perform PA independently. An illustrative example of the possibility of and relation between prehabilitation, rehabilitation during and after treatment, and PA beyond rehabilitation is visualised in **Figure 7.1**. However, this pathway of survivorship care has many scenarios, dependent on different variables, such as physical fitness at the time of diagnosis, the stage and prognosis of the disease, the treatment, and potential complications.

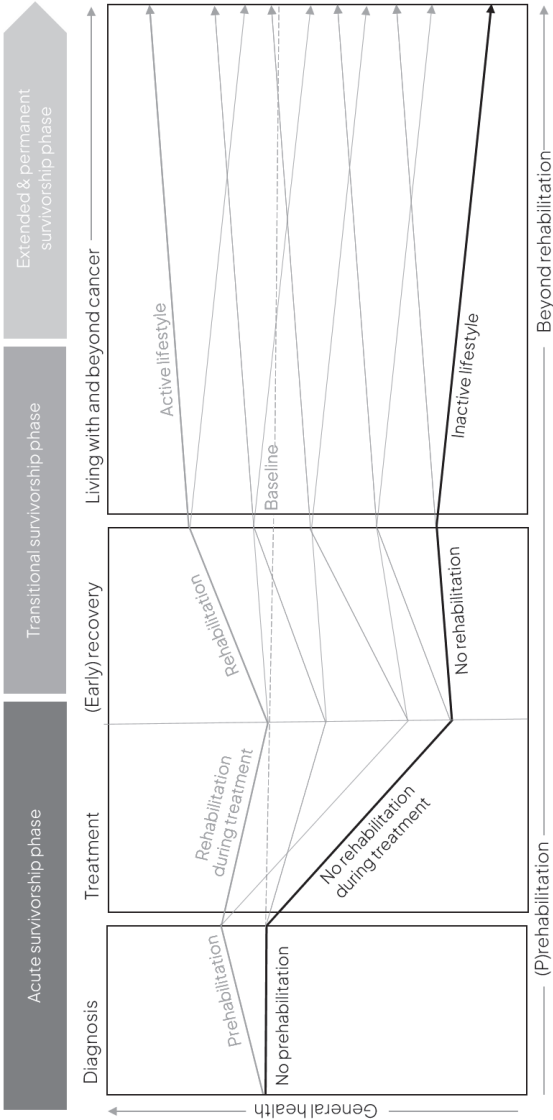


Figure 7.1. An illustrative example of the possibilities of survivorship care in the continuum of the cancer journey: the role of prehabilitation, rehabilitation during and after treatment, and physical activity beyond rehabilitation. As adapted from Simcock et al.³³

Stratification for survivorship care

This thesis focused on cancer survivors who experience interrelated physical and psychosocial complaints and/or fatigue and were therefore referred to multidisciplinary rehabilitation, as recommended in the Dutch Oncology Rehabilitation Guidelines. In these guidelines, it is assumed that approximately 12.5% of all cancer survivors in the Netherlands are in need of multidisciplinary oncology rehabilitation.¹⁰ However, the true numbers of different levels of survivorship care needed and provided remain unknown. Adequate screening and referral are necessary to provide the right survivorship care, at the right time, in the right setting and clinicians have an essential role to “assess, advise and refer”.²³ However, a clear decision tree that can support clinicians in providing cancer survivors with the most suitable survivorship care is lacking. While the multidisciplinary rehabilitation program described in this thesis takes place in a hospital outpatient setting, allied health professionals in primary care have an important role in cancer survivorship as well. Moreover, according to the IZA, public health authorities and community-based initiatives should contribute to improving lifestyle, to keep healthcare accessible and affordable, suggesting that we should look beyond healthcare initiatives.¹² At the Máxima Medical Centre in the Netherlands, a “Medical Specialists’ Exercise Care approach in Oncology” was implemented, using a stratification model for personalised survivorship care.³⁴ Based on this thesis, the stratification model of The Máxima Medical Centre, Dutch Oncology Rehabilitation guidelines, international literature, and our clinical experience, we would propose a stepped-care stratification model of cancer survivorship care into five levels and settings of care, based on the complexity of the patient’s care needs (**Box 7.1**). The process of stratification should be iterative, as cancer survivors’ needs can change throughout the different phases of the patient journey. This also became clear in **Chapter 3**, which indicated that stratification for follow-up care after a supervised exercise program is required, because the ability to maintain PA beyond these programs varies across cancer survivors. This model is mainly focused on exercise, while other allied health professionals and lifestyle interventions (e.g. focusing on psychosocial functioning, nutrition, fatigue, etc.) should be incorporated as well, but are beyond the scope of this thesis. More research is needed to further develop this model in co-creation with other allied health professionals and lifestyle providers and to investigate the effectiveness of this stratification method. This is

discussed in more detail in the paragraph on future research recommendations.

1. **Independent, unsupervised exercise**, for cancer survivors for whom it is safe to and who are able to exercise independently. This is a group of patients who were probably already regularly active before the diagnosis, with high levels of self-efficacy and therefore capable of resuming their exercise routine. Cancer survivors in this group should be provided with information on possibilities for independent exercise, and available digital tools for this (e.g. websites, mobile applications, activity monitors).
2. **Community-based, supervised exercise programs**, for cancer survivors without care needs, for whom it is safe to exercise alone, but with a lack of confidence and self-efficacy to exercise independently. These programs can take place in gyms, with fitness instructors offering exercise programs, in local sports facilities, or remotely like the coaching intervention in *Chapter 3* of this thesis. Municipalities should be stimulated to offer free or low-cost community-based exercise programs for inhabitants.
3. **Primary care, supervised rehabilitation**, with one or more allied health professionals (i.e. physical therapist, occupational therapist, psychologist, social worker, dietician) for cancer survivors with one or more functional complaints that are not interrelated. Ideally, these allied healthcare professionals should collaborate in a network. This level of survivorship care is currently often not (fully) reimbursed by healthcare insurance. In case of increased cardiovascular risk, non-regulated comorbidities, and unexplained complaints during exercise, a consultation with a sports physician should take place before starting the rehabilitation in primary care.
4. **Outpatient, multidisciplinary supervised rehabilitation** aimed at survivors with interrelated physical and psychosocial complaints, requiring a multidisciplinary team under the guidance of a sports or rehabilitation physician. This is also the program described in *Chapter 2* of this thesis.
5. **Outpatient, high complex, multidisciplinary supervised rehabilitation** under close supervision of the rehabilitation physician, for cancer survivors with high complex care needs (e.g., in case of an oncological spinal cord injury or amputation).

Box 7.1. Proposed levels of stratified exercise survivorship care.

Assessment of aerobic capacity

Assessment of impairments is essential for survivorship care stratification. For pro-active survivorship care, regular assessment of physical fitness and patient-reported outcomes should take place from the moment of diagnosis until the phase of permanent survivorship. In the Dutch Oncology Rehabilitation Guidelines, the Distress Thermometer and Problem List (DT&PL), in Dutch known as 'Lastmeter' is recommended to be used for screening of survivorship care needs.¹⁰ However, this questionnaire is broad and generic, aiming to assess the patient's perceived functional, social, spiritual, and physical complaints. Since physical fitness is often severely impaired in cancer survivors^{15,35}, as we also observed in this thesis, and is often targeted in survivorship care, we believe that it is important to monitor physical fitness throughout the cancer journey. As described in the introduction of this thesis, aerobic capacity is an important indicator of physical fitness and could be seen as a 'clinical vital sign', which should be monitored frequently in cancer survivors.³⁶

The criterion standard to monitor aerobic capacity is performing a CPET, requiring expensive, advanced equipment and medical supervision. Given the high pressure on healthcare services and the limited amount of time that healthcare providers can spend with patients consequently, accessible and easy-to-use tools to assess aerobic capacity should be used if possible. Based on the findings of **Chapter 6**, we would recommend using the FitMáx in addition to other questionnaires that are already completed in the consulting room, such as the DT&PL, to get global insight into the aerobic capacity and recognize impairments early on. The benefit of questionnaires is the possibility to monitor outcomes remotely, during phone calls, or using eHealth platforms like e-mails, websites, or mobile applications. If the estimated aerobic capacity is below normative values and cancer survivors are going to participate in an exercise rehabilitation program, it would be recommended to set off then with a performance test to measure aerobic capacity more accurately. In **Chapter 5**, we showed that the SRT is valid to estimate aerobic capacity in cancer survivors and detect improvement when using a cut-off value, which is necessary to prescribe exercise training and monitor progress. However, as also discussed in **Chapters 5 and 6**, it should be kept in mind that the CPET is used to determine the underlying cause of exercise limitations and contra-indications for physical exercise. Therefore, FitMáx and SRT should not be considered full replacements for

the CPET. For cancer survivors with increased cardiovascular risks, such as pre-existing cardiovascular disease, treatment with cardio-toxic chemotherapy, and chest radiation, and cancer survivors with unexplained exertional complaints during exercise (e.g. dyspnoea or fatigue) it would be recommended to start with a CPET under supervision of a sports physician for risk screening and personalised training advice, as is also described in the Dutch Oncology Rehabilitation guidelines.¹⁰ If indicated, a follow-up CPET could be planned for evaluation, or evaluation could be done using the SRT if no abnormalities were observed during the first CPET. Assessment of aerobic capacity could also aid in preoperative risk-stratification and treatment decision-making since preoperative aerobic capacity measured during CPET is related to postoperative outcomes.³⁷ Cuijpers et al. showed that the SRT is also useful for preoperative risk assessment in patients with colorectal cancer, but more research is needed to confirm cutoff values.³⁸

Recommendations for future research

Based on the findings of this thesis, the vision of the MCCC and the IZA, and existing evidence, the following recommendations can be made for future research in the field of oncology rehabilitation.

Improving cancer survivorship care delivery

Although we have extensively described physical fitness and patient-reported outcomes in cancer survivors participating in multidisciplinary oncology rehabilitation in this thesis, insight into cancer survivors who have not been referred to this program is lacking. Research suggests that despite existing Dutch Oncology Rehabilitation guidelines, recognition of functional impairments and subsequent referral to 'the right care in the right place' is not well-implemented in oncology care.^{10,12} In order to optimize referral processes it is necessary to get insight into the survivorship care needs and current referral rates.³⁹ Furthermore, insight into enablers and barriers for clinicians to refer to survivorship care and for patients to take part in survivorship care would help to improve the integration of survivorship care in the patient journey of cancer.

Selecting the right patients and choosing the right interventions

In this chapter, we discussed the importance of stratification and speculated on possible levels of survivorship care. However, more research is needed to identify patients in need of survivorship care at any point in their patient journey, and eventually select the most suitable intervention for them. Larger databases would help to improve the stratification and personalization of survivorship care along the continuum of cancer care nationwide. Sharing data across hospitals and primary care settings in the Netherlands in an overarching data infrastructure would enable us to address the emerging research questions in a large study sample, but this would first require consistency in assessing physical fitness and patient-reported outcomes. If more data are collected on physical fitness and patient-reported outcomes in rehabilitation programs as we did in **Chapter 2**, this would enable us to determine associations between demographic and clinical characteristics and intervention benefits. While less was known about the effectiveness of multidisciplinary oncology rehabilitation at the start of this PhD trajectory, literature on this topic has emerged during the last years. Two recent systematic reviews reported that multidisciplinary oncology rehabilitation programs have positive effects on physical and psychosocial outcomes, even though effects varied greatly across studies.^{40,41} When we are able to identify patients who do not respond ('non-responders') to multidisciplinary rehabilitation as described in the Dutch Oncology Rehabilitation guidelines, we would be aware that these patients need an intervention with a different approach. However, more research would be required then to find the most suitable program for these 'non-responders' afterwards. While training intensity was personalised in the rehabilitation program in this thesis, training frequency, type, and time were equal for all participants and could be more individualized in the future. There is still no consensus on the specific frequency, intensity, type, and time of training (FITT factors) and timing in different patients. Therefore, more research is needed to improve personalised exercise training in cancer survivors with different types and stages of cancer, especially in patients with rare cancers. More specifically, it would be of interest to establish thresholds for the minimum time per week and intensity of PA needed to achieve health benefits and the maximum time and/or intensity to ensure safety for these patients.^{3,16,42,43} As discussed in **Chapters 3 and 4**, stratification for patients in need of follow-

up interventions after supervised rehabilitation would be of added value as well. If we could identify patients at risk for turning inactive following supervised rehabilitation, we could target them for follow-up interventions. More research on effective follow-up interventions for these patients in need should be conducted in the future as well.

Survivorship care: cost-effectiveness and effects on clinical outcomes

While research on cancer survivorship has accelerated, there is still a lack of evidence on the effectiveness on outcomes at healthcare service level, like costs and hospitalization. In a recent review on the cost-effectiveness of exercise in cancer survivors, 10 of the 16 included trials proved cost-effectiveness, but interventions were heterogeneous.⁴⁴ Evidence on healthcare service outcomes for different levels of survivorship care before, during, directly after, and far beyond medical treatment may result in more reimbursement of survivorship care for all patients with different care needs, facilitating the integration of survivorship care along the continuum of cancer care. When looking at cost-effectiveness, social-economical costs should not be forgotten, like the costs that come along with cancer survivors not being able to return to work. Besides, more research is needed to confirm the potentially favourable effect of exercise on cancer recurrence and the development of comorbidities, because this is of great relevance to limiting the increasing pressure on the healthcare system.⁴⁵

To conclude, the findings of this thesis suggest that cancer survivors show improvements in aerobic capacity; muscle strength; levels of fatigue; symptoms of anxiety and depression, and HRQoL, after participating in a 10-week supervised exercise program as part of multidisciplinary rehabilitation. A remote coaching intervention seemed promising to improve PA maintenance beyond completion of the supervised exercise program since it was acceptable to cancer survivors, who also perceived the intervention effective to stimulate PA maintenance. However, the remote coaching intervention was not effective to improve the maintenance of PA levels and to further improve physical fitness and patient-reported outcomes in cancer survivors. The ability to stay active beyond a supervised program seems to vary considerably between cancer survivors and levels of aerobic capacity are still below normative values, six months after completing the exercise program. Aerobic capacity is an

important indicator of physical fitness, which should be monitored regularly from the moment of cancer diagnosis, as a 'clinical vital sign'. This thesis showed that the FitMáx-questionnaire is promising to get global insight into aerobic capacity, while the SRT is more suitable as a performance test to monitor aerobic capacity during exercise rehabilitation. However, the added value of CPET to screen cancer survivors with increased cardiovascular risk and provide training advice should not be overlooked. More research is needed to seek demographic and medical characteristics that can identify cancer survivors in need of survivorship care at any point in their patient journey and provide the personalised care they benefit most from.

It is time to 'move beyond exercise oncology rehabilitation'.

References

1. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. 2020.
2. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
3. Weemaes ATR, Weijenberg MP, Lenssen AF, Beelen M. Exercise training as part of multidisciplinary rehabilitation in cancer survivors: an observational study on changes in physical performance and patient-reported outcomes. *Support Care Cancer* 2022;30(11):9255-9266.
4. van der Steeg GE, Takken T. Reference values for maximum oxygen uptake relative to body mass in Dutch/Flemish subjects aged 6-65 years: the LowLands Fitness Registry. *Eur J Appl Physiol* 2021;121(4):1189-1196.
5. Weemaes ATR, Sieben JM, Beelen M., Mulder LTMA, Lenssen AF. Determinants of physical activity maintenance and the acceptability of a remote coaching intervention following supervised exercise oncology rehabilitation: a qualitative study. *Journal of Cancer Survivorship* 2023;1-13.
6. Weemaes ATR, Beelen M, Bongers BC, Weijenberg MP, Lenssen AF.. Criterion Validity and Responsiveness of the Steep Ramp Test to Evaluate Aerobic Capacity in Survivors of Cancer Participating in a Supervised Exercise Rehabilitation Program. *Arch Phys Med Rehabil*, 2021;102(11):2150-2156.
7. Weemaes ATR, Meijer R, Beelen M, van Hooff M, Weijenberg MP, Lenssen AF et al. Monitoring aerobic capacity in cancer survivors using self-reported questionnaires: criterion validity and responsiveness. *J Patient Rep Outcomes* 2023;7(1): 1-14.
8. Monti S, Grosso V, Todoerti M, Caporali R. Randomised controlled trials and real-world data: differences and similarities to untangle literature data. *Rheumatology (Oxford)* 2018;57(57 Suppl 7):vii54-vii58.
9. Faraoni D, Schaefer ST. Randomised controlled trials vs. observational studies: why not just live together? *BMC Anesthesiol* 2016;16(1):102.
10. National Cancer Institute - Dutch Oncology Rehabilitation Guidelines. 2017.
11. National Cancer Institute. Cancer in the Netherlands - trends & prognoses until 2023. 2022.
12. van Nuenen FM, Donofrio SM, Tuinman MA, van de Wiel HB, Hoekstra-Weebers JE. Feasibility of implementing the 'Screening for Distress and Referral Need' process in 23 Dutch hospitals. *Support Care Cancer* 2017;25(1):103-110.
13. Stout NL, Alfano CM, Belter CW, Nitkin R, Cernich A, Lohmann Siegel K, Chan L. A Bibliometric Analysis of the Landscape of Cancer Rehabilitation Research (1992-2016). *J Natl Cancer Inst* 2018;110(8):815-824.
14. Leclerc AF, Foidart-Dessalle M, Tomasella M, Coucke P, Devos M, Bruyere O. Multidisciplinary rehabilitation program after breast cancer: benefits on physical function, anthropometry and quality of life. *Eur J Phys Rehabil Med* 2017;53(5): 633-642.
15. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;30(20):2530-2537.
16. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon Get al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020;54(24):1451-1462.
17. Goodwin LD, Leech NL. Understanding correlation: Factors that affect the size of r. *The Journal of Experimental Education* 2006;74(3):249-266.
18. Maastricht Comprehensive Cancer Centre Vision 2025. 2021.
19. Ministry of Health, Welfare and Sport. Integrated Healthcare Agreement. 2022.

20. Vaz-Luis I, Masiero M, Cavaletti G, Cervantes A, Chlebowski RT, Curigliano G et al. ESMO Expert Consensus Statements on Cancer Survivorship: promoting high-quality survivorship care and research in Europe. *Ann Oncol* 2022;33(11):1119-1133.
21. Mullan F. Seasons of survival: reflections of a physician with cancer. *N Engl J Med* 1985; 313(4):270-273.
22. Miller K, Merry B, Miller J. Seasons of survivorship revisited. *Cancer J* 2008;14(6):369-374.
23. Schmitz KH, Campbell AM, Stuiver MM, Pinto BM, Schwartz AL, Morris GSet al. Exercise is medicine in oncology: engaging clinicians to help patients move through cancer. *CA Cancer J Clin* 2019;69(6):468-484.
24. Stout NL, Binkley JM, Schmitz KH, Andrews K, Hayes SC, Campbell KLet al. A prospective surveillance model for rehabilitation for women with breast cancer. *Cancer* 2012;118(8 Suppl):2191-2200.
25. Lukez A, Baima J. The Role and Scope of Prehabilitation in Cancer Care. *Semin Oncol Nurs* 2020;36(1):150976.
26. Molenaar CJL, Minnella EM, Coca-Martinez M, Ten Cate DWG, Regis M, Awasthi Ret al. Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery: The PREHAB Randomized Clinical Trial. *JAMA Surg* 2023;158(6):572-581.
27. Renouf T, Bates A, Davis JF, Jack S.. Prehabilitation. An Interdisciplinary Patient-Centric Conceptual Framework. *Semin Oncol Nurs* 2022;38(5):151329.
28. Ligibel JA, ohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SCet al. Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline. *J Clin Oncol* 2022;40(22):2491-2507.
29. Houben LHP, Overkamp M, P VANK, Trommelen J, JGH VANR, P DEV et al. Resistance Exercise Training Increases Muscle Mass and Strength in Prostate Cancer Patients on Androgen Deprivation Therapy. *Med Sci Sports Exerc* 2023; 55(4):614-624.
30. Mijwel S, Bolam KA, Gerrevall J, Foukakis T, Wengstrom Y, Rundqvist H. Effects of Exercise on Chemotherapy Completion and Hospitalization Rates: The OptiTrain Breast Cancer Trial. *Oncologist* 2020;25(1):23-32.
31. van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM et al. Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. *J Clin Oncol* 2015;33(17):1918-1927.
32. Miller R, Northey J, Toohey K. Physical Exercise and Cancer: Exploring Chemotherapy Infusion as an Opportunity for Movement. *Semin Oncol Nurs* 2020;36(5):151068.
33. Simcock R. Principles and guidance for prehabilitation within the management and support of people with cancer in partnership with acknowledgements [Internet]. 2019.
34. van Keeken SM, Dijkstra JW., Vreugdenhil A, van Vessel M, Schep G. Medical Specialists' Exercise Care in Oncology. 2021; Available from: <https://sportengeneeskunde.nl/>.
35. Hurria A, Jones L, Muss HB. Cancer Treatment as an Accelerated Aging Process: Assessment, Biomarkers, and Interventions. *Am Soc Clin Oncol Educ Book* 2016;35: e516-522.
36. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BAet al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* 2016;134(24):e653-e699.
37. Steffens D, Ismail H, Denehy L, Beckenkamp PR, Solomon M, Koh Cet al. Preoperative Cardiopulmonary Exercise Test Associated with Postoperative Outcomes in Patients Undergoing Cancer Surgery: A Systematic Review and Meta-Analyses. *Ann Surg Oncol* 2021;28(12):7120-7146.
38. Cuijpers ACM, Bongers BC, Heldens A, Bours MJL, van Meeteren NLU, Stassen LPS, Lubbers T. et al. Aerobic fitness and muscle density play a vital role in postoperative complications in colorectal cancer surgery. *J Surg Oncol* 2022;125(6):1013-1023.

39. DCS. Strategic presentation on cancer rehabilitation. 2010; Available from: <https://www.cancer.dk/dyn/resources/File/file/1/1561/1385430087/strategicpresentati ononcancerrehabilitationthedanishcancersociety.pdf>.
40. Dennett AM, Sarkies M, Shields N, Peiris CL, Williams C, Taylor NF. Multidisciplinary, exercise-based oncology rehabilitation programs improve patient outcomes but their effects on healthcare service-level outcomes remain uncertain: a systematic review. *J Physiother* 2021;67(1):12-26.
41. Kudre D, Chen Z, Richard A, Cabaset S, Dehler A, Schmid M, Rohrmann S. Multidisciplinary Outpatient Cancer Rehabilitation Can Improve Cancer Patients' Physical and Psychosocial Status—a Systematic Review. *Curr Oncol Rep* 2020; 22(12):122.
42. Bjørke ACH, Sweegers MG, Buffart LM, Raastad T, Nygren P, Berntsen S.. Which exercise prescriptions optimize $\dot{V}O_2\text{max}$ during cancer treatment?—A systematic review and meta-analysis. *Scand J Med Sci Sports* 2019;29(9):1274-1287.
43. Sweegers MG, Altenburg TM, Brug J, May AM, van Vulpen JK, Aaronson NK et al. Effects and moderators of exercise on muscle strength, muscle function and aerobic fitness in patients with cancer: a meta-analysis of individual patient data. *Br J Sports Med* 2019;53(13):812.
44. Wang Y, McCarthy AL, Hayes SC, Gordon LG, Chiu V, Bailey TG et al. Economic evaluation of exercise interventions for individuals with cancer: A systematic review. *Prev Med* 2023;172:107491.
45. Morishita S, Hamaue Y, Fukushima T, Tanaka T, Fu JB, Nakano J. Effect of Exercise on Mortality and Recurrence in Patients With Cancer: A Systematic Review and Meta-Analysis. *Integr Cancer Ther* 2020;19:1534735420917462.



ADDENDUM

Impact paragraph

Summary

Samenvatting

Dankwoord

List of publications

About the author

Impact paragraph

Cancer and its treatment can cause detrimental side effects like impaired physical fitness, mental distress, and chronic fatigue, leading to high healthcare consumption, decreased participation in social activities, and difficulties with returning to work.¹ The increased incidence and improved survival rates of cancer have resulted in a growing population of people living with and beyond cancer (hereafter: cancer survivors) and thereby an increase in societal and financial burden.² The long-standing, complex health issues that cancer survivors are often confronted with, should be addressed with adequate survivorship care, aiming to improve outcomes for the individual patient, but also to decrease the societal and economic burden.^{1,3,4} The Maastricht Comprehensive Cancer Centre (MCCC) aims to provide the best possible oncological care and improve health in the region through the integration of healthcare, scientific research, and education, with a strong focus on ‘survival with preservation of function’.⁵ Because of the increasing pressure on the Dutch healthcare system, the Integrated Healthcare Agreement (in Dutch Integraal Zorgakkoord; IZA) was formulated and published in 2022 as a call for action.⁶ The IZA aims to provide “the right care and support, together with the patient, in the right place and with a focus on health instead of disease”. In this thesis, we reported on research findings about physical fitness and patient-reported outcomes during and beyond a supervised exercise program as part of multidisciplinary oncology rehabilitation. Multidisciplinary rehabilitation consists of exercise training, supplemented by other interventions aiming to improve mental health, chronic fatigue, work reintegration, and nutritional status. In this impact section, we will reflect on the scientific and societal impact of the study results presented by putting this in perspective of the vision of the MCCC and IZA. This was reported according to the Maastricht University Medical Centre (MUMC+) Circle of Innovation, which was developed to stimulate researchers and clinicians to promote healthy living in the region, by accumulating knowledge, innovating healthcare, and creating value for the patient by putting it into practice.

Generating knowledge

This thesis contributed to the body of scientific evidence on multidisciplinary oncology rehabilitation. Results suggested that cancer survivors with interrelated physical and psychosocial complaints have significant and clinically relevant improvements in physical fitness and patient-reported outcomes after participating in a supervised 10-week exercise program, as part of multidisciplinary rehabilitation at the MUMC+. Moreover, findings implicated that higher exercise volumes lead to larger improvements in physical fitness in these patients. The collected data could serve as a reference for other researchers and clinicians since there is not much literature on cancer survivors with interrelated physical and psychosocial complaints.

Another study in this thesis on the effectiveness of remote coaching following supervised exercise rehabilitation has led to novel findings on the long-term outcomes of the exercise program. The results indicated that levels of aerobic capacity remained below normative values at the end of the exercise program and even six months after completion. The potential contribution of telehealth to optimise the sustainability of benefits gained during supervised exercise programs was explored, but a remote coaching intervention was not effective. The transition from supervised rehabilitation to independent physical activity (PA) and the role of remote coaching interventions during this period was also explored from the 'patient perspective' during interviews. These interviews revealed that remote coaching following a supervised exercise program was perceived acceptable to cancer survivors because it stimulated PA maintenance by offering a source of structure, social support, accountability, and confidence. The remote nature of the intervention was perceived as convenient by some of the participants, while others would have preferred additional physical appointments. The ability to maintain PA beyond supervised rehabilitation was related to the level of self-efficacy (i.e. people's belief in their capabilities for performing PA), PA habits, feeling of accountability, physical complaints, and accessibility of PA facilities.

Finally, findings on the usefulness of a practical performance test and self-reported questionnaires to monitor aerobic capacity in cancer survivors were reported. Aerobic capacity is seen as an important component of

physical fitness, reflecting the integrative function of the cardiovascular system, lungs, and muscles, and is therefore considered a 'clinical vital sign' and a good reflection of overall body health. The cardiopulmonary exercise test (CPET) is known as the best available measurement tool to assess aerobic capacity, but is not always feasible because expensive, advanced equipment and medical supervision are required. Moderate agreement between the aerobic capacity measured during a CPET and estimated using the FitMáx®-questionnaire (FitMáx), indicated that this questionnaire is a promising tool to get global insight into aerobic capacity. While a strong correlation between peak work rate achieved during the Steep Ramp test (SRT) and aerobic capacity measured during CPET, suggests that the SRT is suitable as a practical performance test to monitor aerobic capacity during exercise rehabilitation.

In order to have an impact, the knowledge generated during this thesis was also disseminated to researchers and clinicians. Research results have been submitted for publication in open-access, scientific peer-reviewed journals and presented at Dutch and international research conferences. Additionally, findings were shared and discussed with research and physical therapy trainees, and with clinicians, aiming for a direct impact on clinical practice. Moreover, this thesis has led to recommendations for future research in the field of exercise oncology rehabilitation; i.e. improving cancer survivorship delivery, selecting the right patients, choosing the right interventions, and investigating the effectiveness of cancer survivorship care on costs and outcomes at the healthcare services level.

Findings on the usefulness of the SRT to monitor aerobic capacity in cancer survivors were published in the 'Fysiopraxis', which is a Dutch trade journal for physical therapists. Results about the use of the FitMáx to measure aerobic capacity in cancer survivors were shared during a presentation and panel discussion as part of training for members of a national oncology physical therapy network (OncoNet). Research results were also presented and discussed in meetings of the working group 'Oncology Rehabilitation' of the oncology network of the South-East part of the Netherlands (OncoZon).

Innovating healthcare and creating value

The knowledge generated in this thesis has already led to some healthcare innovations as well. Some of these innovations have already been implemented in daily practice, thereby creating value for the cancer survivors involved. For some innovations, follow-up research is required, and/or implementation is still ongoing. Therefore, these two steps of the innovation circle were not always distinct and were described combined.

Standard operating procedures and protocols on the measurement procedures and the execution of the exercise program of the usual care multidisciplinary oncology rehabilitation developed at the start of this PhD project have led to improved agreement and consistency in the process, conduct, and reporting of the exercise program. During the COVID-19 pandemic, the limited accessibility of the onsite rehabilitation program led to a shift in focus towards patients' self-management to PA in their home environment. We developed a home-based resistance exercise training program for the participants in our studies, which is now openly accessible on the website of the MUMC+. However, more research is needed on the implementation of this home-based exercise program.

At the start of this PhD project, a CPET was conducted in all patients before and after the exercise program at the MUMC+. As the short and approachable steep ramp test (SRT) turned out to be able to measure aerobic capacity and detect improvements over time when using a cutoff value, this test is now used to monitor aerobic capacity, while a CPET is performed only before the start of the program, to screen for cardiovascular risk as recommended in the Dutch Rehabilitation Guidelines.⁸ The FitMáx which showed to be valid to estimate aerobic capacity has been implemented in pre-operative risk screening in patients with cancer awaiting abdominal surgery.

The study on the effectiveness of remote coaching following supervised rehabilitation has led to increased attention for long-term PA maintenance at MUMC+. The collaboration with local sports organisation Maastricht Sport and the implementation of their coaching program was initiated during the study and is continued after the completion of the study, despite the null results of the trial in **Chapter 3**. We are currently referring cancer survivors to

Maastricht Sport after the supervised exercise oncology program when they feel unconfident about independent exercise beyond the program and are seeking help with choosing a suitable type of PA. We believe that the remote coaching following supervised exercise oncology rehabilitation could be effective if only survivors in need would be targeted, but more research is needed to prove this. The interviews in **Chapter 4** revealed that cancer survivors appreciated the remote coaching intervention and perceived it to be helpful to stimulate PA maintenance. While the intervention intensity and frequency were consistent in all participants during the study, this is more personalised in practice nowadays. Some cancer survivors receive advice only once, to explore the exercise possibilities provided by Maastricht Sport, when they are not in need of long-term coaching but only need support to choose the exercise activity that suit them best. When patients are still severely impaired and are not capable to perform exercise independently, on the other hand, a coaching trajectory with more face-to-face appointments and physical guidance is possible as well, while these patients were excluded from participation in the study.

Based on the findings of this thesis combined with previous knowledge, a newly developed stratification model for survivorship care was proposed in **Chapter 7**. However, more research is needed to further develop this model and to investigate the effectiveness of this stratification method.

Healthy living

Altogether, the results of this thesis have contributed to improving healthy living among cancer survivors by generating knowledge on the preservation of function and putting some of these findings into practice. We believe that further integration of cancer survivorship care in the continuum of cancer care would be valuable to the entire health system in the region, by preventing treatment complications, cancer progression and recurrence, and decreasing healthcare demand. Additionally, we think that improving the collaboration between oncology care and community-based initiatives could potentially have a societal impact in the future. It could reduce healthcare demand and costs, by improving lifestyle factors in cancer survivors without 'healthcare needs', thereby preventing disease

progression or recurrence and improving healthy living with preservation of function. Maastricht Sport is funded by the municipality of Maastricht and offers sports activities at no cost to improve the healthy living of inhabitants of the Maastricht region. This is in line with the vision of the IZA, which states that community-based initiatives should contribute to improving a healthy lifestyle, to keep healthcare accessible and affordable.⁶ However, more research is needed in the future to stratify cancer survivors for the appropriate level of survivorship care and further investigate the effectiveness of collaboration with community-based initiatives like Maastricht Sport. Finally, we believe that the clinical implications suggested in this thesis can only be further put into practice in collaboration with stakeholders and decision-makers who are in a position to make implementation possible. The contribution of this thesis to each step of the MUMC+ innovation circle is summarised in Figure 1.

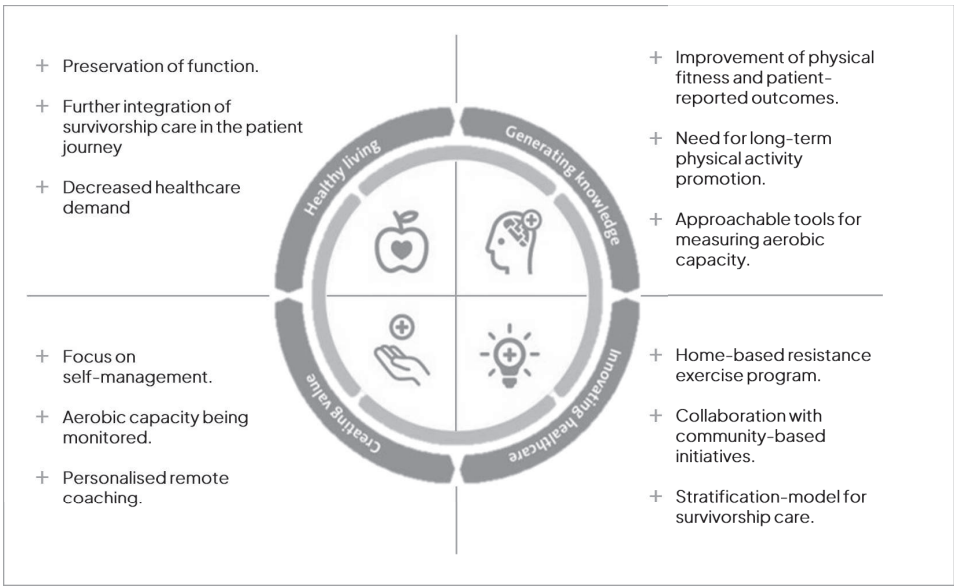


Figure 1. The findings and implications of this thesis summarised in the MUMC+ Circle of Innovation.

During this thesis, we generated and shared knowledge on cancer survivorship care, as the result of embedded research, meaning that there was a fine line between research and clinical practice. Subsequently, we innovated healthcare and created value by putting some of these

innovations into practice and providing implications and recommendations for the future. To finally conclude that we should move beyond exercise oncology rehabilitation to improve healthy living in cancer survivors along the continuum of cancer care.

References

1. Duijts SF, Kieffer JM, van Muijen P, van der Beek AJ. Sustained employability and health-related quality of life in cancer survivors up to four years after diagnosis. *Acta Oncol* 2017;56(2):174-182.
2. National Cancer Institute. Cancer in the Netherlands - trends & prognoses until 2023. 2022.
3. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-2390.
4. Wang Y, McCarthy AL, Hayes SC, Gordon LG, Chiu V, Bailey TG et al. Economic evaluation of exercise interventions for individuals with cancer: A systematic review. *Prev Med* 2023;172:107491
5. Maastricht Comprehensive Cancer Centre. Maastricht Comprehensive Cancer Centre (MCCC) Vision 2025. 2021.
6. Ministry of Health, Welfare and Sport. Integrated Healthcare Agreement. 2022.
7. Oncology Network South-East Netherlands (OncoZON). 2023; Available from: www.oncozon.nl
8. National Cancer Institute - Dutch Cancer Rehabilitation Guidelines. 2017.

Summary

This thesis entitled “Moving beyond exercise oncology rehabilitation” aimed to monitor changes in physical fitness (i.e. aerobic capacity and muscle strength) and patient-reported outcomes (i.e. health-related quality of life (HRQoL); fatigue; anxiety and depression) in cancer survivors during a 10-week supervised exercise program as part of multidisciplinary rehabilitation, optimise the transition to independent long-term PA maintenance, and assess the validity and responsiveness of different methods to monitor aerobic capacity.

In **Chapter 1**, we described the rationale for and the outline of this thesis. The increased incidence and improved survival rates of cancer have led to substantial growth in the number of people living with and beyond cancer. The patient journey of cancer does not end after medical treatment, since patients are often confronted with long-standing side effects like declined physical fitness, chronic fatigue, mental distress, and a diminished HRQoL. Moreover, cancer survivors often suffer from multimorbidity, since modifiable risk factors for developing cancer are also related to other chronic conditions. Altogether, this results in a growing population of cancer survivors, living longer with complex care needs that should be addressed by multidisciplinary survivorship care.

In the Netherlands, guidelines advocate the prescription of a multidisciplinary rehabilitation program for cancer survivors experiencing interrelated physical and psychosocial complaints. While there is abundant literature on exercise in cancer survivors, evidence on multidisciplinary oncology rehabilitation is scarce and the generalisability of research findings to cancer survivors with complex care needs is questionable. Besides, it remains unknown if cancer survivors stay active beyond supervised rehabilitation programs, while this is essential to reach long-term health benefits. Lastly, the importance of measuring aerobic capacity as a ‘clinical vital sign’ throughout the patient journey of cancer has been increasingly recognised, to identify impairments early on. Research on approachable and affordable measurement tools to monitor aerobic capacity is needed to achieve this.

At the Maastricht University Medical Centre (MUMC+), the multidisciplinary oncology rehabilitation program comprises a 10-week group-based, supervised exercise program, supplemented with one or more additional interventions aiming at improving mental health, chronic fatigue, work reintegration, and nutritional status. **Chapter 2** describes the findings of an observational study on this exercise program as part of multidisciplinary rehabilitation. For two years, data from 185 patients participating in the program were collected, thereby giving a realistic reflection of changes in physical fitness and patient-reported outcomes after such programs. Since the exercise program had to be interrupted and later adapted with reduced training time and frequency due to restrictions during the coronavirus-19 (COVID-19) pandemic, we also evaluated the influence of these training adaptations. Results suggested that cancer survivors show significant and clinically relevant improvements in physical fitness and patient-reported outcomes after completion of the supervised exercise program. However, the lack of a randomised control group and therefore the role of the natural course of recovery should be kept in mind when interpreting the changes in outcomes observed. Reduction in training time and frequency during the COVID-19 pandemic resulted in smaller changes in most of the physical fitness outcomes but changes over time remained statistically significant.

In **Chapter 3**, the results of a randomised controlled trial (RCT) on the effectiveness of a remote coaching intervention following a supervised oncology exercise program on improvement of physical activity (PA) levels, physical fitness, and patient-reported outcomes are reported. Ninety-seven participants were recruited from the exercise program as part of multidisciplinary oncology rehabilitation which was described in Chapter 2. Participants were randomised to either the intervention group (n=46), receiving six months of remote coaching, or the control group (n=50), receiving no additional intervention. Measurements of PA levels, physical fitness, and patient-reported outcomes were performed in the first week of the study, which was also the last week of the exercise program, and six months later. Results implicated that remote coaching after participation in a supervised exercise oncology program was not effective to improve the maintenance of PA level and to further improve physical fitness and patient-reported outcomes. A between-group difference of 45 minutes of PA per week suggested that participants who received the remote coaching intervention maintained PA levels slightly better compared to participants

who received no additional intervention, but this difference was not statistically significant. The ability to maintain PA levels after a supervised rehabilitation program varied considerably across participants and was not affected by a remote coaching intervention. Besides, participants reached on average 73% of the normative values for aerobic capacity and 39% of all participants reached values that were even below the lower limit of normal, six months after completing the supervised exercise program.

To be able to optimise interventions and make successful implementation possible, the experiences of the patients in the target group should be incorporated. Therefore, a phenomenological qualitative study was performed in **Chapter 4** to explore the determinants of PA maintenance following supervised exercise oncology rehabilitation and the acceptability of remote coaching during this period. Semi-structured interviews were conducted with a subsample of the participants of the RCT in Chapter 3 and analysed afterward using template analysis. The Capability, Opportunity and Motivation model of behaviour (COM-B model) was used as a theoretical framework to get insight into determinants of PA maintenance following supervised exercise rehabilitation. Self-efficacy, PA habits, accountability, physical complaints, and facilities were key themes that were perceived to influence PA maintenance. The Theoretical Framework of Acceptability (TFA) was used to assess the acceptability of the remote coaching intervention investigated in Chapter 3. Remote coaching was perceived as acceptable because it stimulated PA maintenance by offering a source of structure, social support, accountability, and confidence. The remote nature of the intervention was perceived as convenient by some of the participants, while others would have preferred additional physical appointments. In conclusion, remote coaching following supervised exercise programs was considered acceptable to cancer survivors but should be personalised and should focus on improving self-efficacy and habit-formation, in order to help patients to overcome PA barriers like physical complaints and limited accessibility of PA facilities.

The second part of this thesis focused on the methodology of measuring aerobic capacity.

Chapter 5 aimed to assess the validity and responsiveness of a short, practical performance test on a cycle ergometer, called the steep ramp test (SRT). Participants were recruited from the supervised exercise program as

described in Chapter 2 and performed the cardiopulmonary exercise test (CPET) and SRT before and after the program. Peak work rate achieved during the SRT (SRT-WR_{peak}) was compared with peak oxygen consumption measured during the CPET (CPET-VO_{2peak}), which is the criterion standard for aerobic capacity. Given the strong correlation ($r=0.86$) between SRT-WR_{peak} and CPET-VO_{2peak}, the SRT proved to be valid to estimate aerobic capacity in cancer survivors. The correlation between changes in CPET-VO_{2peak} and SRT-WR_{peak} after completing the exercise program ($r=0.51$) indicated that the responsiveness to estimate changes in aerobic capacity over time was moderate. Receiver operating characteristic analysis showed that the SRT was able to detect improvement in aerobic capacity (area under the curve (AUC)=0.74) when using a cutoff value of 0.26 watts per kg bodyweight.

In **Chapter 6**, the validity and responsiveness of the self-reported Duke Activity Status Index (DASI), Veterans Specific Activity Questionnaire (VSAQ), and the FitMáx®-questionnaire (FitMáx) to monitor aerobic capacity in cancer survivors were assessed. The FitMáx was recently developed to estimate aerobic capacity based on the self-reported maximum capacity of walking, stair climbing, and cycling combined with demographic characteristics. Participants were again recruited from the exercise program as described in Chapter 2, and completed the three self-questionnaires on the same day they performed a CPET, before and after the 10-week exercise program. Results showed that the agreement between CPET-VO_{2peak} and VO_{2peak} estimated using the questionnaires (questionnaire-VO_{2peak}) was moderate for the FitMáx (intraclass correlation coefficient (ICC)=0.69) and VSAQ (ICC=0.53), and poor for DASI (ICC=0.36). Poor agreement between changes in CPET-VO_{2peak} and changes in questionnaire-VO_{2peak} show that all questionnaires had poor responsiveness to monitor changes in aerobic capacity (ICC of 0.43, 0.19, and 0.18, for FitMáx, VSAQ, and DASI, respectively). However, the FitMáx was able to detect change in aerobic capacity (AUC 0.77) with an optimal cutoff value of 1.0 mL/kg/min, while the DASI (AUC=0.64) and VSAQ (AUC=0.66) were not. Values for validity and responsiveness were better for FitMáx compared to DASI and VSAQ.

In **Chapter 7**, we summarised the main findings of this thesis and reflected on methodological considerations, implications for clinical practice, and future research recommendations. The pros and cons of the used study designs were discussed and the potential influence of the study population

and the COVID-19 pandemic on the study results were discussed. Clinical implications were discussed in the context of the missions of the Maastricht Comprehensive Cancer Centre (MCCC) and the Integrated Healthcare Agreement (in Dutch: Integraal Zorgakkoord; IZA), leading to a suggestion for a stepped-care stratification model of cancer survivorship care. Finally, we speculated on future research directions, with the overall object of integrating personalised cancer survivorship care along the continuum of cancer, by selecting the right patients and choosing the right interventions.

To conclude, the findings of this thesis suggest that cancer survivors with interrelated physical and psychosocial complaints show improvements in physical fitness and patient-reported outcomes after participating in a 10-week supervised exercise program as part of multidisciplinary oncology rehabilitation. Results showed that remote coaching is not effective to improve PA maintenance and further improve physical fitness and patient-reported outcomes beyond completion of supervised exercise programs, but is acceptable to cancer survivors, who perceived the intervention as effective to stimulate PA maintenance. The ability to maintain PA varies across cancer survivors and levels of aerobic capacity remain below healthy levels in a significant part of the cancer survivors, six months after completing the remote coaching intervention. Finally, the findings of this thesis suggested that the FitMáx is promising to get global insight into aerobic capacity, while the SRT is more suitable as a performance test to monitor aerobic capacity during exercise rehabilitation when performing CPET is not feasible or indicated.

Samenvatting

Het doel van dit proefschrift getiteld "*Moving beyond exercise oncology rehabilitation*" was het in kaart brengen van veranderingen in fysieke fitheid (aerobe capaciteit en spierkracht) en patiënt-gerapporteerde uitkomsten (gezondheidsgerelateerde kwaliteit van leven; vermoeidheid; angst en depressie) bij mensen die leven met en na kanker (hierna: *cancer survivors*) tijdens een fysiek trainingsprogramma als onderdeel van multidisciplinaire oncologische revalidatie, het optimaliseren van de overgang naar zelfstandig bewegen op de lange termijn en het bepalen van de validiteit en responsiviteit van verschillende meetinstrumenten voor het monitoren van aerobe capaciteit.

In **Hoofdstuk 1** hebben we de aanleiding en de opzet van dit proefschrift beschreven. De toegenomen incidentie en verbeterde overlevingskansen van kanker hebben geleid tot een substantiële groei van het aantal *cancer survivors*. De *patient journey* van kanker eindigt niet na de medische behandeling, aangezien patiënten vaak worden geconfronteerd met langdurige bijwerkingen, zoals een verminderde fysieke fitheid, chronische vermoeidheid, psychische problematiek en een verminderde gezondheidsgerelateerde kwaliteit van leven. Bovendien is er bij patiënten met kanker vaak sprake van multimorbiditeit, omdat beïnvloedbare risicofactoren voor het ontwikkelen van kanker ook gerelateerd zijn aan andere chronische aandoeningen. Al met al resulteert dit in een groeiende populatie van *cancer survivors*, die langer leven met complexe zorgbehoeften die vragen om multidisciplinaire nazorg.

Nederlandse richtlijnen adviseren een multidisciplinair revalidatieprogramma voor *cancer survivors* met samenhangende lichamelijke en psychosociale klachten. Hoewel er veel literatuur is over fysieke training bij *cancer survivors*, is het bewijs voor multidisciplinaire oncologische revalidatie schaars en zijn de onderzoeksresultaten mogelijk niet te generaliseren naar *cancer survivors* met complexe zorgbehoeften. Bovendien is het onbekend of *cancer survivors* hun activiteitsniveau kunnen behouden na afloop van gesuperviseerde revalidatieprogramma's, terwijl dit essentieel is om gezondheidsvoordelen op de lange termijn te kunnen bereiken. Tot slot wordt het belang van het monitoren van aerobe capaciteit als een 'klinische vitale parameter' gedurende het gehele

oncologische traject steeds meer erkend, om zo beperkingen vroegtijdig te kunnen identificeren. Daarvoor is onderzoek nodig naar laagdrempelige en betaalbare meetinstrumenten om aerobe capaciteit te monitoren.

In het Maastricht Universitair Medisch Centrum (MUMC+) bestaat het multidisciplinaire oncologische revalidatieprogramma uit een 10 weken durend gesuperviseerd fysiek trainingsprogramma in groepsverband, aangevuld met één of meer interventies gericht op het verbeteren van de mentale gezondheid, chronische vermoeidheid, arbeidsre-integratie en voedingstoestand. **Hoofdstuk 2** beschrijft de bevindingen van een observationele studie naar dit trainingsprogramma als onderdeel van multidisciplinaire revalidatie. Gedurende twee jaar werden gegevens verzameld van 185 patiënten die deelnamen aan het programma, waardoor een realistische weergave kon worden gegeven van veranderingen in fysieke fitheid en patiënt-gerapporteerde uitkomsten na dergelijke programma's. Het trainingsprogramma moest worden onderbroken en later aangepast met een lagere trainingstijd en -frequentie, vanwege beperkingen tijdens de coronavirus-19 (COVID-19) pandemie. Daarom evalueerden we ook de invloed van deze trainingsaanpassingen. Resultaten suggereren dat *cancer survivors* significante en klinisch relevante verbeteringen in fysieke fitheid en patiënt gerapporteerde uitkomsten laten zien na deelname aan een 10 weken durende gesuperviseerde trainingsprogramma. Daarbij moet echter wel het ontbreken van een gerandomiseerde controlegroep en als gevolg daarvan de rol van het natuurlijke beloop van herstel in gedachten worden gehouden, bij het interpreteren van de waargenomen verbeteringen in uitkomsten. Vermindering van de trainingstijd en -frequentie tijdens de COVID-19 pandemie resulteerde in kleinere veranderingen in de meeste uitkomsten van fysieke fitheid, maar de veranderingen over de tijd bleven statistisch significant.

In **Hoofdstuk 3** worden de resultaten beschreven van een gerandomiseerde gecontroleerde studie (RCT) naar de effectiviteit van een coaching interventie op afstand voor het verbeteren van behoud van fysieke activiteitsniveaus, fysieke fitheid en patiënt gerapporteerde uitkomsten, na afloop van een gesuperviseerd oncologisch trainingsprogramma. Zevenennegentig deelnemers werden geworven uit het trainingsprogramma als onderdeel van multidisciplinaire oncologische

revalidatie dat in Hoofdstuk 2 werd beschreven. De deelnemers werden gerandomiseerd naar de interventiegroep (n=46), die 6 maanden coaching op afstand kreeg, of naar de controlegroep (n=50), die geen extra interventie ontving. Metingen van fysieke activiteitsniveaus, fysieke fitheid en patiënt-gerapporteerde uitkomsten werden uitgevoerd in de eerste week van het onderzoek, wat tevens de laatste week van het trainingsprogramma was, en zes maanden later. Resultaten impliceerden dat coaching op afstand na deelname aan een gesuperviseerd oncologisch trainingsprogramma niet effectief was voor het verbeteren van behoud van fysieke activiteitsniveaus en het verder verbeteren van de fysieke fitheid en patiënt-gerapporteerde uitkomsten. Een verschil van 45 minuten fysieke activiteit per week tussen de groepen suggereerde dat deelnemers die de coaching op afstand ontvingen hun fysieke activiteitsniveaus iets beter konden behouden in vergelijking met deelnemers die geen extra interventie kregen, maar dit verschil was niet statistisch significant. Het vermogen om fysieke activiteitsniveaus te behouden na een gesuperviseerd revalidatieprogramma varieerde aanzienlijk tussen de deelnemers en werd niet beïnvloed door een coaching interventie op afstand. Bovendien bereikten de deelnemers gemiddeld maar 73% van de normwaarden voor aerobe capaciteit en 39% van alle deelnemers bereikte waarden die zelfs onder de ondergrens van normaal lagen, zes maanden na het afronden van het gesuperviseerde trainingsprogramma.

Om interventies te kunnen optimaliseren en een succesvolle implementatie mogelijk te maken, moeten ervaringen van de patiënten in de doelgroep worden meegenomen. Daarom werd in **Hoofdstuk 4** een fenomenologische kwalitatieve studie uitgevoerd om inzicht te krijgen in determinanten van behoud van fysieke activiteitsniveaus na afloop van een gesuperviseerd oncologisch revalidatieprogramma en de aanvaardbaarheid van coaching op afstand in deze periode. Er werden semigestructureerde interviews afgenomen met een deel van de deelnemers uit de RCT in Hoofdstuk 3, welke achteraf geanalyseerd werden met behulp van template analyse. Het *Capability, Opportunity en Motivation model of behaviour* (COM-B model) werd gebruikt als theoretisch kader om inzicht te krijgen in determinanten van behoud van fysieke activiteitsniveaus na afloop van gesuperviseerde trainingsprogramma's. Zelf-effectiviteit, beweeg gewoonten, gevoel van verantwoordelijkheid door 'een stok achter de deur', fysieke klachten en

beweeg faciliteiten waren belangrijke thema's waarvan werd ervaren dat deze invloed hadden op behoud van fysieke activiteitsniveaus. Het *Theoretical Framework of Acceptability* (TFA) werd gebruikt om de aanvaardbaarheid van de in Hoofdstuk 3 onderzochte coaching interventie op afstand te beoordelen. Coaching op afstand werd als aanvaardbaar ervaren, omdat patiënten het gevoel hadden dat het behoud van fysieke activiteitsniveaus gestimuleerd werd door het bieden van structuur, sociale steun, een gevoel van verantwoordelijkheid en zelfvertrouwen. Het feit dat de interventie op afstand plaatsvond, werd door sommige deelnemers als prettig ervaren, terwijl anderen de voorkeur gaven aan de toevoeging van fysieke afspraken. Concluderend was coaching op afstand na een gesuperviseerd trainingsprogramma aanvaardbaar voor *cancer survivors*. Dit zou gepersonaliseerd aangeboden moeten worden en zou zich moeten richten op het verbeteren van zelf-effectiviteit en gewoontevorming, om patiënten te helpen barrières voor behoud van fysieke activiteitsniveaus te overwinnen, zoals fysieke klachten en beperkte toegankelijkheid van beweegfaciliteiten.

Het tweede deel van dit proefschrift richtte zich op de methodologie van het meten van aerobe capaciteit.

Het doel van **Hoofdstuk 5** was om de validiteit en responsiviteit van een korte, praktische inspanningstest op een fietsergometer, genaamd de steep ramp test (SRT), te bepalen. Deelnemers werden geworven uit het gesuperviseerde trainingsprogramma zoals beschreven in Hoofdstuk 2 en voerden de cardiopulmonale inspanningstest (CPET) en SRT voor en na het programma uit. De hoogst behaalde weerstand die werd bereikt tijdens de SRT (SRT-WRpiek) werd vergeleken met de hoogst gemeten zuurstofopname tijdens de CPET (CPET-VO₂piek), welke de criterium standaard is voor het meten van aerobe capaciteit. Gezien de sterke correlatie ($r=0,86$) tussen SRT-WRpiek en CPET-VO₂piek, bleek de SRT valide om aerobe capaciteit te evalueren bij *cancer survivors*. De correlatie tussen verandering in CPET-VO₂piek en SRT-WRpiek na het afronden van het trainingsprogramma ($r=0,51$) suggereerde dat de responsiviteit om veranderingen in de tijd te meten matig was. *Receiver operating characteristic* analyse liet zien dat de SRT in staat was om verbetering in aerobe capaciteit te detecteren (*area under the curve* (AUC) 0,74) bij gebruik van een afkapwaarde van 0,26 watt per kg lichaamsgewicht.

In **Hoofdstuk 6** werden de validiteit en responsiviteit van de zelf-gerapporteerde Duke Activity Status Index (DASI), Veterans Specific Activity Questionnaire (VSAQ) en de FitMáx©-vragenlijst (FitMáx) voor het monitoren van aerobe capaciteit bij *cancer survivors* beoordeeld. De FitMáx werd onlangs ontwikkeld om aerobe capaciteit te schatten op basis van de zelf-gerapporteerde maximale capaciteit van wandelen, traplopen en fietsen in combinatie met demografische kenmerken. Deelnemers werden opnieuw geworven uit het trainingsprogramma zoals beschreven in Hoofdstuk 2, en vulden de drie zelfvragenlijsten in op dezelfde dag dat ze een CPET uitvoerden, voor en na het 10 weken durende trainingsprogramma. De resultaten toonden aan dat de overeenkomst tussen CPET-VO₂piek en VO₂piek geschat met behulp van de vragenlijsten (vragenlijst-VO₂piek) matig was voor de FitMáx (*intraclass correlatie-coëfficiënt* (ICC)=0,69) en VSAQ (ICC=0,53), en slecht voor de DASI (ICC=0,36). De slechte overeenkomst tussen veranderingen in CPET-VO₂piek en veranderingen in vragenlijst-VO₂piek laat zien dat alle vragenlijsten een slechte responsiviteit hadden om veranderingen in aerobe capaciteit te kunnen meten (ICC van 0,43, 0,19 en 0,18 voor respectievelijk FitMáx, VSAQ en DASI). De FitMáx was echter wel in staat om verandering in aerobe capaciteit te detecteren (AUC=0,77) met een optimale afkapwaarde van 1,0 mL/kg/min, terwijl de DASI (AUC=0,64) en VSAQ (AUC 0,66) dat niet waren. De waarden voor validiteit en responsiviteit waren beter voor FitMáx in vergelijking met DASI en VSAQ.

In **Hoofdstuk 7** hebben we de belangrijkste bevindingen van dit proefschrift samengevat en reflecteerden we over de methodologische overwegingen, implicaties voor de klinische praktijk en aanbevelingen voor toekomstig onderzoek. De voor- en nadelen van de gebruikte onderzoeksdesigns werden besproken en de mogelijke invloed van de studiepopulatie en de COVID-19 pandemie op de studieresultaten werden besproken. Klinische implicaties werden beschreven in de context van de missies van het Maastricht Comprehensive Cancer Centre (MCCC) en het Integraal Zorgakkoord (IZA), wat leidde tot een voorgesteld *stepped-care* stratificatiemodel van beweegzorg bij *cancer survivors*. Tot slot speculeerden we over de richting voor toekomstig onderzoek, met als overkoepelend doel het integreren van gepersonaliseerde revalidatie zorg voor *cancer survivors* gedurende het oncologische traject, door het selecteren van de juiste patiënten en het kiezen van de juiste interventies.

Concluderend suggereren de bevindingen van dit proefschrift dat cancer survivors met onderling samenhangende lichamelijke en psychosociale klachten verbetering laten zien in fysieke fitheid en patiënt-gerapporteerde uitkomsten na deelname aan een 10 weken durend gesuperviseerd trainingsprogramma als onderdeel van multidisciplinaire oncologische revalidatie. De resultaten lieten zien dat coaching op afstand niet effectief is voor het verbeteren van behoud van activiteitsniveaus en het verder verbeteren van fysieke fitheid en patiënt-gerapporteerde uitkomsten na afloop van gesuperviseerde trainingsprogramma's, maar wel acceptabel is voor *cancer survivors*, die de interventie als effectief ervaren voor het stimuleren van behoud van fysieke activiteit. Het vermogen om actief te blijven na afloop van een gesuperviseerd trainingsprogramma varieert tussen *cancer survivors* en aerobe capaciteit blijft onder gezonde waarden voor een aanzienlijk deel van de deelnemers. Tot slot liet dit proefschrift zien dat de FitMáx veelbelovend is om globaal inzicht te krijgen in aerobe capaciteit, terwijl de SRT als inspanningstest meer geschikt is om de aerobe capaciteit te evalueren tijdens fysieke trainingsprogramma's, wanneer het uitvoeren van CPET niet haalbaar of geïndiceerd is.

Dankwoord

“In life, it’s not where you go, it’s who you travel with.” | Charles M. Schulz

En dan nu echt het laatste hoofdstuk van deze reis, het dankwoord. Terwijl ik dit schrijf, kan ik haast nog niet geloven dat ik straks eindelijk een echt boekje in mijn handen heb. Mijn boekje, maar dit was natuurlijk nooit gelukt zonder heel veel mensen om me heen. Daarom wil ik iedereen die hieraan bijgedragen heeft ontzettend bedanken en in dit hoofdstuk enkele mensen in het bijzonder.

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List of publications

Weemaes ATR, Beelen M, Weijenberg MP, van Kuijk SMJ, Lenssen AF. *Effects of remote coaching following supervised exercise oncology rehabilitation on physical activity levels, physical fitness, and patient-reported outcomes: a randomised controlled trial*. International Journal of Behavioral Nutrition and Physical Activity. In press.

Weemaes ATR, Sieben, JM, Beelen M, Mulder LTMA, Lenssen AF. *Determinants of physical activity maintenance and the acceptability of a remote coaching intervention following supervised exercise oncology rehabilitation: a qualitative study*. Journal of Cancer Survivorship, 2023; 1-13.

Weemaes ATR*, Meijer R*, Beelen M, van Hoof M, Weijenberg MP, Lenssen AF, van de Poll-Franse LV, Savelberg HHCM, Schep G. *Monitoring aerobic capacity in cancer survivors using self-reported questionnaires: criterion validity and responsiveness*. Journal of Patient-Reported Outcomes, 2023; 7(1): 73. *shared first authorship

Weemaes ATR, Weijenberg MP, Lenssen AF, Beelen M. *Exercise training as part of multidisciplinary rehabilitation in cancer survivors: an observational study on changes in physical performance and patient-reported outcomes*. Supportive Care in Cancer, 2022; 30(11): 9255-9266.

Weemaes ATR, Beelen M, Bongers BC, Weijenberg MP, Lenssen AF. *Criterion validity and responsiveness of the steep ramp test to evaluate aerobic capacity in survivors of cancer participating in a supervised exercise rehabilitation program*. Archives of Physical Medicine and Rehabilitation, 2021; 102(11): 2150-2156.

van Dijk-Huisman HC, **Weemaes ATR**, Boymans TAEJ, Lenssen AF, de Bie RA. *Smartphone app with an accelerometer enhances patients' physical activity following elective orthopedic surgery: a pilot study*. Sensors, 2020; 20(15), 4317.

About the author

Anouk Tanja Rudy Weemaes was born on July 27th 1994 in Terneuzen, the Netherlands. After completing secondary school at the Reynaertcollege in Hulst in 2012, she moved to Maastricht to pursue a bachelor's degree in Physical Therapy at Zuyd Hogeschool in Heerlen (2012–2015). In 2015, she started working part-time as a physical therapist at Integrated Care Limburg, while engaging in a master's program in Human Movement Sciences (2015–2016). During the last six months of her master's study, she went to Canada to write her thesis during a research internship at the Human Performance Lab at the University of Calgary.

After obtaining her master's degree in 2016, she commenced working at the Department of Physical Therapy at the Maastricht University Medical Centre (MUMC+). Initially, she worked full-time as a hospital-based physical therapist, but later on, she began combining her clinical work with doing research. As a physical therapist, she specialised in treating patients with oncological and neurological disorders. In 2018 she initiated her PhD project on exercise oncology rehabilitation while continuing her work as a physical therapist. Her PhD project aimed at monitoring changes in physical fitness and patient-reported outcomes during a supervised exercise oncology program, optimising the transition to independent long-term physical activity maintenance, and assessing the validity and responsiveness of different methods to monitor aerobic capacity in cancer survivors. During her PhD project, she also specialised in conducting and analysing cardiopulmonary exercise tests. Her supervision team consisted of prof. dr. Ton Lenssen (promotor), prof. dr. Matty Weijenbergh (promotor) and Milou Beelen (co-promotor). Currently, Anouk is continuing her work as physical therapist and embedded scientist at the Department of Physical Therapy at the MUMC+.

