Review Article

Exercise training in cancer related cardiomyopathy

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Abstract: The therapeutic options for malignancies have been expanding over the past decades. Since the rise of targeted therapies, improved survival rates and decreased morbidity of cancer patients are evident but these refined protocols have steadily increased the number of patients at risk for long-term side-effects of anti-neoplastic treatments. The leading causes of death in cancer survivors are now defined by cardiovascular disease. Thus, there is a growing need for understanding how cancer related cardiovascular diseases such as cardiomyopathies or vasculopathies develop and how this can be prevented. Besides classical symptoms of heart failure with or without decompensation, an overwhelming majority of cancer patients develop fatigue and a significant reduction in exercise capacity when compared to their pre-cancer state. These effects seem to be independent from the specific chemotherapeutic substance included in the treatment regimen. Recent trials have suggested beneficial effects of exercise regiments in early and late phases of cancer treatment regimens and during rehabilitation. This review focuses on the currently available literature and evidence for the role of exercise training in preventing declining cardiac function or improving an already impaired function during or after chemotherapy, radiation or other cancer-specific therapies.

Keywords: Cardiomyopathy; cancer; exercise; chemotherapy; heart failure

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Introduction

The development of new medical therapies in oncology over the past decades is an impressive success and has fundamentally changed the outcome of cancer patients. Improved diagnostic algorithms and an increasing arsenal of modern and novel therapies allowed achieving higher rates of remission and cancer-free survival for many malignancies. As a result, a significant improvement in survival rates is evident and the medical community is confronted with a larger number of patients who have a history of oncological treatment and are at risk for related cardiac complications (1). If expressed in numbers, one can see an increase in the overall 5-year survival rates for all cancers in the United States that rose from around 50% in the late seventies to 69% in the past decade (1).

However, this apparent success is accompanied by a growing number of cancer survivors who face the consequences of the chemotherapeutic regimens and novel therapies with a wide range of unintended side effects. One of the biggest issues due to its mortality-defining nature is the wide range of cardiac and cardiovascular toxicities affecting the entire cardiovascular-skeletal muscle axis (2,3). This affects not only patients currently in treatment but also patients with preexisting cardiovascular conditions going into therapy. This is considerably noteworthy because many forms of cancer share almost all risk factors with cardiovascular diseases (4). For example, a recent community-based study showed an inverse relation between cancer incidence and the absence of seven predefined

cardiovascular risk factors as defined by the AHA (5). One of the worst complications of chemotherapeutic treatments is the development of chemotherapy-related cardiomyopathy (CRC) which can develop years if not decades following the initial treatment. The mortality rate in cancer survivors with cardiomyopathies is significantly higher than for idiopathic non-ischemic cardiomyopathy. A study in 2000 found a 3.5-fold increase in mortality for doxorubicin induced cardiomyopathy compared to idiopathic non-ischemic cardiomyopathy. The significance of the issue was highlighted in a cohort study published in 2011 that showed that the leading cause of mortality for breast-cancer survivors was cardiovascular even surpassing the relapsing underlying malignant condition (6).

To address the need of adequate screening, prevention and treatment of CRC the term "cardio-oncology" has been coined as preventing heart failure in patients paramount for their long-term health not only because of the increased cardiovascular mortality but also because worsening cardiac function may limit their possibility to receive adequate cancer treatment (7,8). Unsurprisingly, the involvement of a cardiologist in most stages of cancer treatment in terms of a multidisciplinary approach is recommended more and more frequently in current guidelines (9). Moreover an overwhelming amount of cancer survivors suffer from a reduction in quality-of-life related to symptoms of fatigue, nausea, pain and depression occur frequently. Studies also show that exercise capacity as measured in cardio-pulmonary exercise testing is reduced in approximately 70% of cancer patients (10).

This review focuses on the currently available evidence for the role of exercise training in preventing declining cardiac function or improving an already impaired function during or after chemotherapy, radiation or other cancer-specific therapies.

Cancer-related cardiomyopathy

Cancer-related cardiomyopathy (CRC) is a condition with very heterogeneous underlying pathomechanisms due to the varying modes of action of the suspected causing drug (11). Ewer and Lippman introduced a general classification in 2005 which is based on the presence or absence of structural abnormalities and the extent of functional reversibility. Subsequently CRC is classified in an injury type with permanent loss of function (Type 1) and a dysfunction type with temporarily and often reversible loss of cardiac function (Type 2) (12). Even though this classification seems appealing recent MRI studies showing scar formations in Type 2 patients and improving cardiac function with guideline directed medical therapy (GDMT) in presumed Type 1 patients have called the validity of the classification into question (13,14). A more recent attempt at defining CRC suggested the diagnostic criteria as a decrease in left ventricular ejection fraction (LVEF) by 5% or more to less than 55% in the presence of symptoms of heart failure or an asymptomatic decrease in LVEF by 10% or more to less than 55% (15).

The list of drugs suspected or proven to cause CRC is long and probably growing with the continuing introduction of modern novel therapy protocols. One of the best studied and well-established drugs classes are probably anthracyclines usually causing permanent structural changes. Also anthracycline induced CRC is occurring quite frequently and is usually associated with a poor prognosis (16,17). Among other substance classes that can cause structural cardiac impairment are high-dose alkylating agents and small-molecule tyrosine kinase inhibitors (18). The class of monoclonal antibody-based tyrosine kinase inhibitors most famously trastuzumab can be described as the "prototype substance" for Type 2 CRC, as the impaired cardiac function usually improves with discontinuation of the therapy. Interestingly the incidence of CRC in patients treated with trastuzumab is higher when concurrently treated with anthracyclines (19). The recent addition of checkpoint inhibitors targeting CTLA-4 (ipilimumab), PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab, durvalumab, avelumab) show also next to promising results in cancer therapy a significant rate of cardiotoxic side effects. A list with selected substance classes and examples can be found in *Table 1*.

Another prominent mode of cardiovascular damage associated with cancer therapy is radiation-induced CRC. It's noteworthy that radiation usually induces a spectrum of cardiomyopathies that differ from the chemotherapy-induced CRCs mentioned before. Frequent presentations are acute pericarditis, chronic pericarditis and myocardial fibrosis. These changes can occur with a delay up to 30 years after chest radiation (20). Improvements in involved-field radiation techniques and refined CT-based radiation planning reduced the incidence in recent years.

Exercise training in cancer related cardiomyopathy

If looking at effects of exercise training in CRC it is worth reviewing data from the general population first. Although it

Table 1 List of selected substance classes and example substance with known cardiotoxicity

Substance class	Substance
Anthracyclines	Doxorubicin
	Epirubicin
	Idarubicin
	Mitoxantrone
Alkylating agents	Cyclophosphamide
	Ifosfamide
	Busulfan
	Mitomycin
Antimetabolites	Clofarabine
	5-fluorouracil
	Capecitabine
	Cytarabine
Antimicrotubule agents	Vincristine
Monoclonal antibody-based tyrosine kinase inhibitors	Bevacizumab
	Trastuzumab
	Pertuzumab
	Alemtuzumab
Small-molecule tyrosine kinase inhibitors	Dasatinib
	Imatinib
	Lapatinib
	Sunitinib
	Sorafenib
	Pazopanib
Proteasome inhibitor	Bortezomib

seems like an obvious truism that regular exercise is beneficial for healthy individuals and patients with cardiovascular diseases alike, there is objective data to support it. Regular physical activity does reduce the risk of cardiovascular morbidity and mortality (21). Furthermore, a fairly recent prospective cohort study enrolling 416,175 subjects showed a long-term benefit even for people who exercise moderately (approximately 90 minutes per week) compared to inactive individuals with a 14% reduced risk of all-cause mortality and a 3-year longer life expectancy. With increased activity, this effect could be improved even further (22).

When talking about systolic heart failure in general, exercise training has shown to be beneficial also in secondary prevention. The most notable and recent randomized trial was the HF-ACTION trial that enrolled 2,331 patients and randomized them to either standard medical care or standard care plus a supervised exercise regimen of 90 minutes per week. In the median follow up of about two and a half years, a non-significant reduction in mortality could be observed (23). Along these findings a Cochrane systematic review and meta-analysis published in 2016 also suggested a significant reduction in all-cause mortality and recurrent hospitalization for patients with exercised based structured rehabilitation compared to no-exercise controls (21). This data is reflected in a class I recommendation for patients with coronary heart disease and a class IIa recommendation for patients with chronic systolic heart failure in the current AHA/ACCF guidelines (24).

When looking at trials conducted during cancer treatment, the overwhelming majority of available evidence stems from trials conducted in woman with breast cancer. Since the therapy protocols frequently involve anthracyclines, cyclophosphamide and monoclonal antibody-based tyrosine kinase inhibitors as well as chest radiation this data might be specific for the distinct class of chemotherapeutic regimen and type of cancer.

Exercise training before cancer therapy

Preclinical trials conducted with mice showed a benefit for exercise training before initiating a potentially cardiotoxic therapy (25). This concept (also dubbed "pre-habilitation") seems intuitively appealing. By improving the functional cardiorespiratory capacity and activity levels beforehand, one might argue that the following functional decline might be alleviated or the development of heart failure even prevented altogether.

One trial published in 2014 evaluated a multimodal structured pre-habilitation protocol including moderate aerobic and resistance exercises, nutritional counseling with protein supplementation, and relaxation exercises. One group started the protocol 4 weeks before abdominal surgery for colorectal cancer while the other group started immediately after surgery. The authors showed a meaningful change in postoperative functional exercise capacity (26). However, to date there are no randomized trials evaluating a structured exercise regimen in the time period between diagnosis and the initiation of a specific systemic chemotherapy with respect to mortality or development of heart failure.

Exercise training during cancer therapy

Even though many trials are comparatively small in their sample size most of them report a positive effect in peak oxygen uptake (VO_2peak) as well as a reduction in fatigue and improvement in quality-of-life or other parameters of cardio-respiratory fitness. However, a notable issue besides the heterogeneity of the underlying disease is therapy adherence even in controlled study environments. Some trials report adherence rates as low as 59%. A list of selected clinical trials during cancer therapy is listed in *Table 2*.

The general picture even though mostly supportive is not exclusively positive. One fairly recent randomized trial enrolled 101 participants and followed those patients for about one year. The authors could not report a significant improvement in physical functioning. However, this trial only included women with metastatic disease whereas the other trials could show the benefit for exercise therapy in patients with early-stage breast cancer (46). Additionally, no randomized controlled trials or phase III trials are available to address end-points beyond cardio-respiratory fitness. A single study reported next to an increase in VO_2peak an improvement in vascular endothelial function in the brachial artery (39). Furthermore even though there is no data that supports an actual harm of exercise therapy during ongoing cancer treatment, most trials do not systematically report safety endpoints.

Exercise training after cancer therapy

Evidence from phase III trials from exercise training during cancer therapy is not available yet. Observational studies however tend to show positive results for an active lifestyle. One trial published by Jones *et al.* in 2016 conducted a prospective cohort study that enrolled 2,973 women with non-metastatic breast cancer and followed them for a median of about 8.5 years. The authors could show an inverse relationship between exercise intensity and incidence of cardiovascular events in general and of coronary artery disease and heart failure in particular. In the multivariate analysis, the association did not differ according to age, CVD risk factors, menopausal status, or anticancer treatment (47). In young adults, this benefit might even be larger as reported in a trial enrolling 15,450 adult survivors of childhood cancer. This trial could report after a median follow-up of 10 years, comparing low physical activity (<3 MET-h·wk–1) and increased physical activity (≥3 MET-h·wk–1), a reduction in all-cause (19%), recurrence/progression (39%) of the underlying malignant disease or and health-related deaths (11%) (48).

Beyond observational data, most trials report end points limited to cardio-respiratory fitness. For example, a recent trial enrolled 152 breast cancer survivors participating in cardiac rehabilitation for 22 weeks. The authors could show improvements in health-related quality-of-life and depression as well as an improvement in VO_2peak by 14% (49).

Several trials report an improvement in cardio-respiratory fitness. For example, one trial published in 2017 showed among 63 survivors of testicular cancer that high-intensity aerobic interval training improved cardiovascular parameters such as arterial thickness, arterial stiffness, post-exercise parasympathetic reactivation, inflammation, and low-density lipoprotein when compared to usual care (50). A list of selected clinical trials during cancer therapy is listed in *Table 3*.

Future studies

As of today there are several trials recruiting that might further our understanding. For example, the Exercise to Prevent AnthraCycline-based Cardio-Toxicity Study 2.0 (EXACT 2, NCT03748550) aims to enroll 100 patients with breast cancer to be randomized either to standard care or aerobic exercise training. The primary outcome measure will be change in LV function while change in cardiac biomarkers such as hs-TNT and N-terminal pro b-type natriuretic peptide are among the secondary endpoints. The trial is not expected to be completed until 2023.

Another study to look forward to regarding cardiovascular endpoints for patients undergoing cancer therapy is the Multidisciplinary Team IntervenTion in CArdio-Oncology trial (TITAN, NCT01621659). The authors aim to enroll nearly 300 participants with breast cancer or lymphoma and randomize to either standard care or to a multidisciplinary team-intervention consisting of cardiologists, clinical nutritionists, pharmacists, exercise physiologists and physiotherapists. Since the primary and secondary endpoints of this trial will be changes in longitudinal LV strain as well as heart failure associated biomarkers this trial might be able to identify subclinical changes in cardiac function. Furthermore smaller wearable activity monitors might help to improve the quality of the obtained data and possibly include more patients in future trials (56).

Conclusions

As of today there is only limited evidence that exercise

Table 2 Selected trials investigating exercise intervention during active cancer treatment

Study	Malignancy	N	Intervention	Outcome
MacVicar *et al.* [1989] (27)	Stage II breast cancer	45	Supervised aerobic exercise: 60–85% of maximum heart rate for 3 days/week and 10 weeks	Increase in VO_2peak with aerobic exercise
Segal *et al.* [2001] (28)	Stage I/II breast cancer	123	Exercise at 50–60% of VO_2peak for 5 days/week and 26 weeks	Increase in VO_2peak with supervised exercise
Kolden *et al.* [2002] (29)	Stage I–III breast cancer	40	20 minutes of aerobic exercise at 70% VO_2max for 3 days/week and 16 weeks	Increase in VO_2peak; reduction in depression and systolic blood pressure
Drouin *et al.* [2006] (30)	Stage 0–III breast cancer	20	Supervised moderate aerobic exercise for 7 weeks	Increase in VO_2peak and red blood cell count
Kim *et al.* [2006] (31)	Stage 0–III breast cancer	41	30 minutes supervised aerobic exercise at 60–70% of VO_2peak for 3 days/week and 8 weeks	Increase in VO_2peak; reduction in resting heart rate and blood pressure
Courneya *et al.* [2007] (32)	Stage I–IIIa breast cancer	242	Supervised aerobic exercise at 60–80% VO_2peak, 15–45 min/day for 3 days/week and 17 weeks	Increase in VO_2peak
Courneya *et al.* [2009] (33)	Lymphoma	122	Supervised aerobic exercise at 60–100% VO_2peak for 3 days/week and 12 weeks	Increase in VO_2peak
Segal *et al.* [2009] (34)	Prostate cancer	121	Supervised aerobic exercise or resistance therapy for 3 days/weeks and 24 weeks	Increase in VO_2peak for resistance therapy compared to usual care
Haykowsky *et al.* [2009] (35)	Stage I–IIIa breast cancer	17	Supervised aerobic exercise at 60–90% of VO_2peak, 30–60 min/day for 3 days/week and 4 months	No change in VO_2peak, blood pressure, left ventricular ejection fraction or left ventricular diameters
Ligibel *et al.* [2010] (36)	Stage I–III breast cancer	41	Moderate exercise at 55–80% of maximum heart rate for 120 minutes/week and 12 weeks	Increase in VO_2peak and quality of life
Noble *et al.* [2012] (37)	Breast cancer; colorectal cancer; hematological malignancy	386	60 minutes of aerobic exercise twice weekly for 12 weeks	Decrease in systolic and diastolic blood pressure
Courneya *et al.* [2013] (38)	Stage I–IIIa breast cancer	301	Standard exercise (30 min/day) *vs.* high exercise (50–60 minutes/day) *vs.* combined exercise (aerobic exercise for 25–30 min/day and 2 sets of resistance exercise)	No significant difference in VO_2peak between high and standard exercise
Jones *et al.* [2013] (39)	Breast cancer	20	Aerobic exercise at 55–100% VO_2peak for 3 days/week and 12 weeks	Increase in VO_2peak and flow-mediated dilation
Vincent *et al.* [2013] (40)	Stage I–III breast cancer	42	Home-based walking program at 50–60% of maximum heart rate for 3 days/week and 12 weeks.	Increase in VO_2peak and 6-minute walk test distance
Hornsby *et al.* [2014] (41)	Stage IIb–IIIc breast cancer	20	Supervised aerobic exercise, 15–45 min/day at 60–70% of VO_2peak for 3 days/week and 12 weeks	Increase in VO_2peak
Travier *et al.* [2015] (42)	Breast cancer	204	Supervised aerobic and strength exercise, 60 min/day for 2 days/week and 18 weeks	No significant difference in VO_2peak
Grabenbauer *et al.* [2016] (43)	Breast cancer; gastrointestinal cancer	45	Supervised aerobic exercise, 30–60 min/day for 3 days/week for 3–12 months	Increase in VO_2peak in the first 3 months, after neither decline nor increase
Cornette *et al.* [2016] (44)	Stage I–IIIB breast cancer	44	Home-based adapted physical activity program, 20–40 min/day for 3 days /week and 27 weeks	Increase in VO_2peak in the first 3 months, after neither decline nor increase
Scott *et al.* [2018] (45)	Breast cancer with metastatic disease	65	Aerobic exercise at 55–100% VO_2peak for 3 days/week and 12 weeks	No significant difference in VO_2peak

Table 3 Selected trials investigating exercise intervention after active cancer treatment

Study	Malignancy	N	Intervention	Outcome
Courneya *et al.* [2003] (51)	Breast cancer survivors	53	Aerobic exercise, 15–35 minutes for 3 days/week and 15 weeks	Increase in VO_2peak
Pinto *et al.* [2013] (52)	Colorectal cancer survivors	46	Aerobic exercise, 10–30 minutes for 2–5 days/week and 48 weeks	Increase in VO_2peak
Jones *et al.* [2014] (53)	Cancer survivors with signs of heart failure after therapy	90	Aerobic exercise, 20–45 minutes for 4 days/week and 52 weeks	No difference inVO_2peak between aerobic exercise and usual care
Jones *et al.* [2014] (54)	Prostate cancer 75 d after therapy	50	Aerobic exercise, 30–45 minutes for 2–5 days/week and 48 weeks	Increase in VO_2peak and flow-mediated dilation
Rogers *et al.* [2015] (55)	Breast cancer survivors	222	Aerobic exercise, 15–50 minutes for 3–5 days/week and 12 weeks	No difference inVO_2peak between Aerobic exercise and usual care
Adams *et al.* [2017] (50)	Testicular cancer survivors	63	Aerobic exercise, 35 minutes for 3 days/week and 12 weeks	Increase in VO_2peak, carotid intima-media thickness, carotid distensibility

therapy can actually prevent or mitigate CRC. However, there is plenty of evidence to support the importance of exercise in cancer treatments in order to improve cardio-respiratory fitness of patients during and after cancer treatment. This significantly improves typical treatment associated symptoms such as fatigue which is an important end-point for patients and physicians alike. However, it cannot be a suitable surrogate parameter for actually improving cardiac function or decreasing cardiovascular mortality.

As the number of patients with malignancy and the number of patients surviving cancer treatment is expected to rise, large and randomized prospective trials will be needed to evaluate the safety, intensity and efficacy of exercise training in the different stages of cancer treatment. More importantly cardiovascular endpoints such as re-hospitalization due to heart failure, death due to cardiovascular causes or echocardiographic parameters defining the ventricular function need to be reported in order to better attribute any effect to an improvement of CRC.

The need of an interdisciplinary approach for patients as complex as cancer patients with an ever increasing number of available substances, improving survival rates and. Therefore, the field of onco-cardiology will become more and more important in an aging population with a rising prevalence of multimorbidity.

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Footnote

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