

Targeted Exercise Training for Cancer Patients: Moving beyond Generic Exercise Guidelines in Clinical Oncology

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Abstract

The field of exercise oncology has rapidly evolved over the past 30 years. Initial investigations of safety and feasibility have progressed towards efficacy and effectiveness trials with a variety of health-related outcomes in mind. More recently, it has been recognized that interventions aimed at modifying physical activity behavior (i.e. behavioral interventions to increase participation in un/structured physical activity) are distinctly different from those aiming to target a clinically relevant outcome (using a specific exercise prescription). There is a strong rationale for the latter, where cancer/treatment toxicities can result in musculoskeletal, cardiopulmonary, and/or hematological declines with important prognostic implications. Treatment intolerance, unfavorable tumor response and heightened risk of mortality are all consequences of leaving these impairments unaddressed. Importantly, the control/reversal of the decline in these systems is more likely to occur through a targeted exercise prescription, specifically designed to target the impairment, rather than interventions trying to change behavior. This requires careful consideration in the study design in exercise oncology in relation to the selection of clinically relevant outcomes, decisions on methods of assessments and ensuring the exercise is targeted to the outcome.

The objective of this review is to 1) conceptualize and provide a clinical rationale for targeted exercise interventions in exercise oncology, and 2) provide a framework for consideration in the design and execution in targeted exercise interventions in oncology. We hope that this framework can encourage research into targeted exercise interventions in oncology and that our framework can be used to inform the design of future trials.

Keywords:

Introduction

Clinical oncology has encountered an exponential increase in research initiatives into the application of exercise interventions over the last 30 years^{1,2}. As a supportive care and/or rehabilitation strategy, exercise training has been proposed to address almost every conceivable outcome in cancer patients, including, but not limited to, weight loss², cardiopulmonary fitness³, body composition⁴, sleep quality⁵, and depression⁶. In turn, a range of national and international societies and agencies have published

cancer-specific exercise guidelines, mirroring, to a large extent, physical activity guidelines in healthy individuals^{1,2,7}. Accordingly, exercise guidelines are now universally promoted as holistic rehabilitation and broad-spectrum health promotion in individuals with a cancer diagnosis, on par with that of healthy individuals and other (chronic) pathologies^{1,7}.

While the overall public health implications of these guidelines should not be underestimated, generic exercise programming may only in part fulfil the potential of exercise training in oncology. Today, there are strong indications that deterioration in specific organ systems, e.g. cardiopulmonary, musculoskeletal and hematological declines, constitute critical obstacles in cancer patient management^{3,8-12}. Indeed, physiological impairments can result in a worse prognosis, either through increas-

ing the risk of treatment complications and/or toxicities, or by causing significant side/late effects that influence health-related quality (and quantity) of life in post-treatment survivorship¹³⁻¹⁵. Theoretically, many of these pathophysiological changes are controllable or reversible by exercise training. However, generic exercise programs are unlikely to optimally counter any of them, and individual patients may have highly specific needs of such programs, calling for a more targeted approach^{16,17}.

Against this background, we present the concept of ‘targeted exercise training’ as a novel and fundamentally different strategy to generic exercise guidelines/programs in the oncology setting. We argue there is an untapped potential in utilizing a targeted approach, in contrast to the universal ‘exercise-for-all’ strategy, by targeting specific physiological systems with exercise training in selected ‘at risk’ individuals in settings, where such intervention, if successful, has more realistic (and larger) impact on treatment tolerability and/or efficacy. In this topical review, we outline the overall conceptual rationale of targeted exercise interventions, followed by a proposed operational framework for the promotion and integration of targeted exercise prescription in exercise oncology research and practice.

Conceptualizing targeted exercise training in cancer

The nature of exercise involves bouts of strenuous exertion, which challenges whole-body homeostasis and provokes widespread adaptations in numerous cells, tissues and organs¹⁸. It is therefore not surprising that exercise is championed as a ‘do-it-all’ health promoting strategy, as this pleiotropic impact can be of great significance in a public health context. However, it is important to distinguish between a public health perspective that is universal promotion of physical activity or exercise behavior, i.e. getting ‘populations’ to be more active, and the setting of individual treatment within clinical medicine in a critical disease population, such as the oncology setting. Here, well-defined, specific and individual treatment objectives/targets drive meticulous treatment decisions for individual patients, and treatments are utilized if, there is plausible and realistic reason to think they will impact relevant tumor and/or pathophysiology without being overwhelmed by detrimental side effects. Thus, in the setting of cancer treatment per se, it is important to consider how, and to which extent, a wide range of possible exercise effects may influence this complex balance between treatment specific effects and side effects.

Clinical relevance and treatment implications

Advances in detection and development of new and aggressive treatment strategies has led to overall improved potential for tumor control, but also derives secondary clinical challenges

of potential relevance for exercise oncology^{19,20}. Certain treatments, e.g. cisplatin-based chemotherapy for testicular germ cell cancer, radiotherapy for head and neck cancer, androgen-deprivation therapy (ADT) for locally advanced prostate cancer, are so effective that cancer control can generally be expected¹⁹. However, improved cancer-specific prognosis often comes at the expense of significant physiological deterioration in off-target organ systems, e.g. cardiovascular toxicities, muscle dysfunction and loss of metabolic control^{3,8-11}. This, typically treatment-specific decline is often of such magnitude that patients physiologically ‘age’ several decades over the course of just weeks/months of treatment (Fig. 1)²¹, and ultimately becomes the most significant health problem in post-treatment survivorship, increasing the risk of developing comorbidities, cancer-related and all-cause mortality²²⁻²⁴. For example, in women with early stage breast cancer undergoing anthracycline-based adjuvant chemotherapy, significant cardiac toxicities are almost universally observed manifesting in lower cardiac function and approximately 30% lower cardio-pulmonary fitness compared to sedentary age-matched women with no cancer history²⁵. These ‘secondary’ health challenges to anti-cancer therapy are suggested to drive the early onset of cardiovascular events, which has been shown to surpass breast cancer as the main cause of mortality from approximately 7 years after treatment^{26,27}.

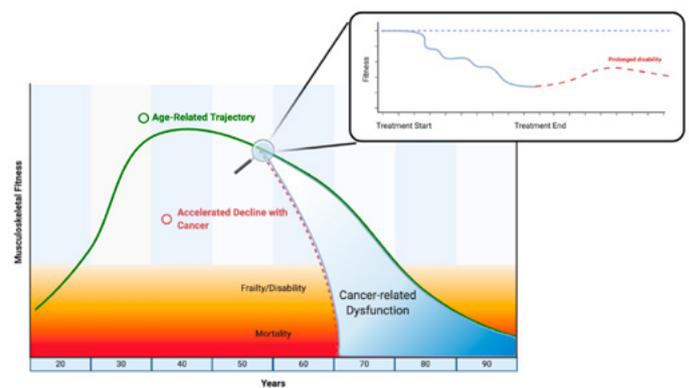


Fig. 1 The theoretical consequence of cancer and its treatments on accelerated aging. Cancer and its treatments induce distinct and pronounced physiological decrements in months that mirrors those changes associated with years/decades of natural aging. This “cancer-related dysfunction” can continue to worsen even after treatment cessation, exacerbating physiological decline, resembling an accelerated biological aging. Created with BioRender.com

In other clinical settings, potentially effective treatment strategies are either contraindicated, or come with significant increased risk of serious complications in patients with specific pre-existing pathophysiological characteristics. Low levels of fitness are associated with major post-operative complications and may even result in critical treatment options being contraindicated (as in the case of low VO_2 peak and surgery for lung resection)^{28,29}. Patients scheduled for radical gastrointestinal tumor

resection can be deemed inoperable due to poor performance status, and patients with low muscular function (sarcopenia) are known to present with significantly increased risk of serious post-operative complications³⁰. Further still, performance status (i.e. Karnofsky Performance Status or Eastern Cooperative Oncology Group) scales have been used as eligibility criteria for clinical trials, which limit access to potentially beneficial treatments for vulnerable groups³¹. It should be noted that there is ongoing conversation surrounding the utility of performance status scales as indicators of treatment decisions and trial eligibility^{31,32}. Nevertheless, as it stands, targeting individuals with low functioning in accordance with these scales may result in the availability of more treatment options and potentially reduce the complications/toxicities associated with treatment.

Moreover, dysfunction in off-target organ systems is commonly reported throughout different treatment trajectories with pre-specified adjustments to the treatment protocols. For example, neutropenia, a common side effect of many cytotoxic treatments, can cause delays, dose reduction or early termination in the scheduled protocol with subsequent negative implications for long term treatment efficacy³³. In these scenarios (Fig. 2), a specific intervention targeting the ‘limiting factor’ or serious late effect would theoretically lead to improvements in treatment outcomes.

Exercise training theoretically has the capacity to reverse and improve these physiological impairments, many of which are now identified as ‘treatment limiting factors’. Thus, it is possible that exercise modifiable endpoints can be identified and targeted in an attempt to optimize treatment outcomes. However, it is also clear that exercise prescription, progression and evaluation are largely specific and need to be tailored, adapted and individualized for such specific impairments/outcomes in different settings. This stands somewhat in contrast to the traditional application of exercise training in the oncology setting, where generic exercise programs (e.g. 150 min moderate intensity aerobic activity per week) are applied without specific outcomes in mind. While such interventions can lead to positive effects on various outcomes, it is far from certain that the given outcome is of a critical nature (at least in the population studied), nor that the changes are clinically meaningful in magnitude.

Differentiating physical activity, generic exercise programs from targeted exercise training

The word ‘targeted’ in targeted exercise prescription alludes to its purpose of specificity in relation to a clinically relevant impairment/outcome of interest, and helps to differentiate it

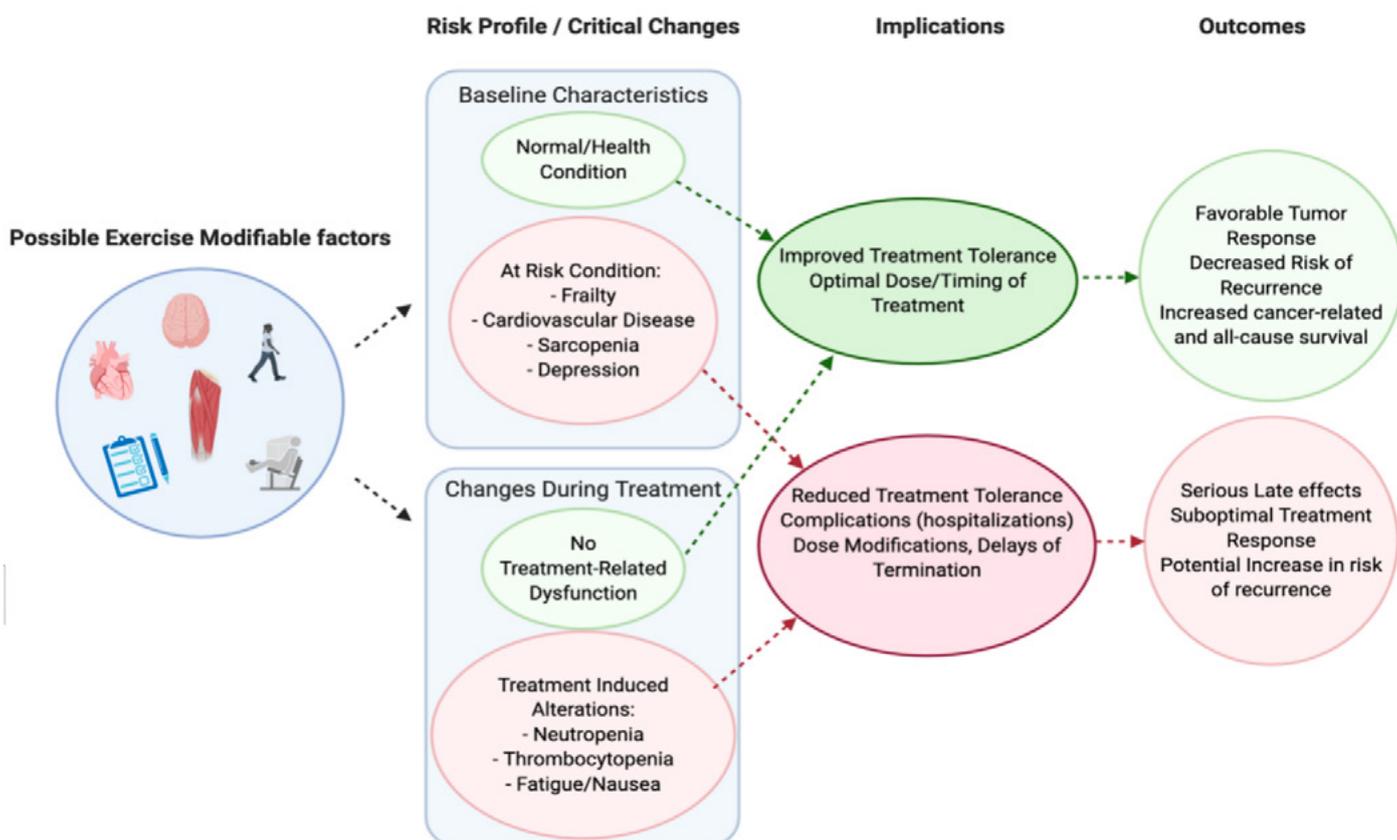


Fig. 2 Potential implications of baseline fitness characteristics and treatment related alterations on treatment response and prognosis. Targeting at risk populations or intervening to reduce the incidence/severity of treatment induced alterations in fitness has potential to alter or improve this pathway. Created with BioRender.com

from efforts to increase physical activity from a more holistic health perspective³⁴. While any type of physical activity can beneficially replace sedentary time, recent reports demonstrate that the detrimental impact of high levels of sedentary time is countered by adequately high levels of high intensity activities and also emphasize that certain exercise adaptations are not achieved through generic activities^{35,36}. Thus, it is readily clear, that the challenge of reducing sedentary time differs markedly from that of engaging people in structured exercise training with moderate to high intensities.

Importantly, exercise training can be further differentiated and targeted to specific outcomes. A recent global characterization of the human plasma metabolome in response to endurance and resistance training revealed distinct profiles³⁷, as these different exercise modalities elicit distinct physiological perturbations. Thus, from a ‘prescription’ perspective, different exercise characteristics (dose, intensity) and principles of training (specificity, progressive overload, periodization, etc.) can be utilized to customize programs to reach specific objectives with relevance for oncology patient management (Fig. 3).

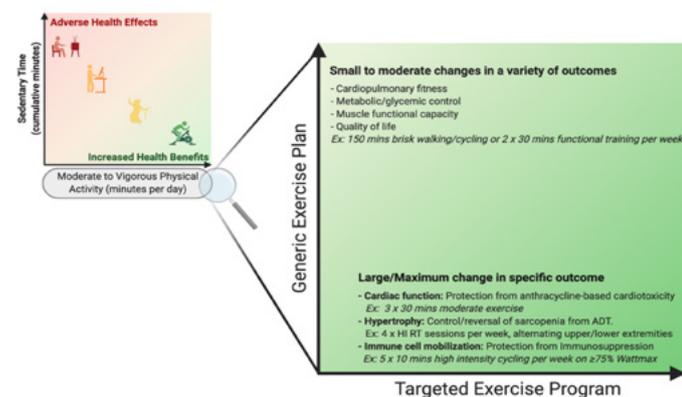


Fig. 3 Differential health outcomes associated with sedentary behavior, physical activity and targeted exercise, extending the framework. Based on data from Ekelund et al³⁵ and from the latest US physical activity guidelines³⁶, differentiating the health effects of low/high sedentary time from low/high levels of moderate-to-vigorous activity. Here, moderate-to-vigorous activities can comprise generic exercise plans influencing multiple outcomes with small to moderate response, or targeted programs maximizing response for a specific outcome. Min, minutes; HI RT, high intensity resistance training. Created with BioRender.com

Arguments can be made in most cancer settings for interventions aiming to 1) promote activity (minimize sedentary time), 2) utilize generic exercise programs (overall health benefits), and 3) targeted exercise training (targeting specific impairments/outcomes). However, such interventions have different aims, comprise very different content, and should be designed and evaluated accordingly³⁴. Moreover, it needs to be acknowledged that these interventions, to a large extent, ‘exclude’ each other, and careful consideration should be made when deciding

the ultimate aim of an intervention. For example, loss of bone mineral density and muscle mass are common occurrences in breast and prostate cancer^{38,39}. Increasing physical activity participation (through walking or dragon boat racing, for example) can be a meaningful outcome for improving some elements of health and well-being, though are unlikely to provide an appropriate or sufficient stimulus to reverse muscle and bone loss⁴⁰. In contrast, a 6–12 month high-load resistance training program with impact exercise may result in the maintenance or improvement of bone mineral density but may not be rooted in fundamental theories of behavior change that are central to the adoption and maintenance of habitual exercise. One of the key distinguishing factors between interventions aimed at promoting activity and those with targeted outcomes is the selection of primary outcomes. The promotion of physical activity usually takes the form of a behavior change trial, where the primary outcome is a change in physical activity behavior or habits (step counts, reduced sedentary time, attendance at exercise sessions, etc.). The nature of targeted exercise interventions in oncology relies on the overarching objective to modulate a specific exercise dependent outcome (e.g. muscular strength, cardiovascular fitness, depressive symptoms), which, at least observationally, comprises a critical factor within a given clinical setting for optimizing the treatment trajectory. In the following sections, we provide a framework for the design of targeted exercise interventions in oncology.

Operational framework for targeted exercise training

Our proposed framework has three primary foci: 1) the identification of clinically relevant endpoints and populations, 2) considerations about evaluations, assessments and anticipated magnitude of change, and 3) structuring the exercise intervention to optimize the potential change in outcomes. While it may follow that this process is sequential, these foci are all interrelated and require careful consideration as changes in one will influence the others.

Determine intermediate endpoints–modifiable by exercise

Defining a clinically relevant outcome that has the potential to be influenced by exercise is a critical step in the targeted approach. These decisions should be made with foundational physiological and psychological concepts in mind; namely, there needs to be a sufficiently strong rationale to support the hypothesis that exercise would influence the outcome. For example, evidence from years of research indicates that there is strong rationale and underlying physiology to support that aerobic exercise can positively influence the cardiovascular

system⁴¹. However, bone pain that arises from osteoblastic bone metastases in advanced cancer is unlikely to be positively impacted by adaptations from exercise training⁴². As such, there should be a logical (and realistic) rationale as to how exercise participation or adaptations may result in meaningful changes in the outcome of interest.

There are a variety of well-documented impairments from tumor- and/or treatment-related factors in cancer that have the potential to be modified through targeted exercise. Cardiovascular remodeling, sarcopenia, bone loss and cancer-related fatigue, amongst others are all commonly reported in individuals with cancer, even months and years after treatment⁴³⁻⁴⁸. Importantly, there is continued discussion on when the best time is to intervene in these individuals, with the consensus generally being as early as possible to reduce either the risk of occurrence or the magnitude/severity of impairments. Herein, it would be beneficial to identify individuals at risk for various impairments (i.e. individuals receiving anthracycline chemotherapy are at a heightened risk of cardiotoxicity) and apply proactive/protective targeted exercise to reduce the risk of occurrence or magnitude of severity. Importantly, these decisions should not be made in isolation. It should be noted though, that 'as early as possible' may not always be appropriate or feasible. The pre-surgical setting is often touted as the 'pre-habilitation' stage of exercise oncology with promising potential, but comes with a host of challenges, most notably the time between diagnosis and treatment and the immediate emotional, financial and relational burden on the patient. This burden, in addition to sometimes limited windows between diagnosis and treatment can impact the feasibility and effectiveness of exercise training.

The treatment period itself can also vary dramatically across tumor types and disease stages, which has important implications for adherence, retention and potential change in desired outcomes. Head and neck cancer for example has a notoriously burdensome treatment schedule, with radiation and/or weekly chemotherapy across 6 weeks, often resulting in pronounced weight loss, muscle wasting, reduced physical function and increased fatigue⁴⁹. Capozzi et al compared a 12-week exercise intervention offered during treatment (ILI) for head and neck cancer, to the same intervention that was delayed until after treatment (DLI)⁵⁰. Their results revealed the ILI was unsuccessful at preventing disease/treatment-related declines in body composition and noted poor adherence as a potential explanation (38.7% of ILI attending >58% of weekly exercise classes compared to 65.5% of DLI). These results highlight the need for important conversations on *when* is the most appropriate time of intervention with important considerations on participant burden, logistics and potential feasibility.

Interventions aimed at trying to reduce the incidence and/or magnitude of impairments are distinct from those aiming to target a specific impairment that has already occurred, with

the latter being woefully underresearched in the exercise oncology world. For example, it has been noted that the literature examining the impact of exercise on cancer-related fatigue is impacted by the lack of studies that specifically screen for and use confirmation of cancer-related fatigue as the eligibility criteria⁵¹. This lack of consistency in screening/recruiting individuals with cancer-related fatigue in interventions targeting fatigue in cancer has contributed to the inconsistency in results supporting the benefit of exercise for cancer-related fatigue. An extreme analogy of this could be studies investigating exercise interventions in cardiovascular disease or diabetes and enrolling apparently healthy individuals. It is likely that they stand to benefit, but the contribution of these study designs to evidence of the impact of exercise for cardiovascular disease or diabetes will be negligible. As such, an important conversation in the design stage of exercise oncology trials is the desire to either reduce the incidence/magnitude of impairments in *at risk individuals* or to try and ameliorate impairments by recruiting, screening and enrolling participants *with a documented impairment*.

Ultimately, arrival at clinically relevant endpoints in exercise oncology should result from conversations with both patient advisory groups and key medical staff to ensure that outcomes are in fact clinically relevant. Within this concept, several questions related to the selection of endpoints already alluded to above are worth considering: 1) *What* (is the outcome clinically relevant with sufficient rationale to be modified through exercise); 2) *Who* (is the outcome specific to a diagnosis or common across different cancers); 3) *When* (is the most appropriate time to intervene that will optimize the likelihood of an exercise effect on the outcome). These questions are highlighted in Table 1. Understanding the underlying framework can increase the likelihood of selection of clinically relevant outcomes that can be modified through exercise and are intervened in at an appropriate time.

Evaluation considerations

Upon consensus of relevant physiological or psychosocial endpoints, which are deemed most important and timely to target with exercise training, there are important considerations as to most appropriately monitor/evaluate changes in said outcome. Multiple considerations factor into the ultimate selection of assessment methods, i.e. available time frame and resources, level of accuracy needed, and potential risks, e.g. with invasive procedures or radiation-based imaging techniques, etc. It is beyond the scope of this review to give a detailed overview and discussion of methodological considerations in exercise oncology, but some important points should be highlighted with specific relevance in the design and execution of targeted exercise training.

Table 1 Key questions in the selection of a primary outcome for targeted exercise in oncology

Question	Concept	Example scenario	Considerations
What	Physiological or psychosocial impairment with a rationale for exercise as an intervention. Does it have potential to be modified with targeted exercise?	Sarcopenia is a common occurrence during and after treatments for cancer.	The magnitude, severity and mechanisms of sarcopenia vary across tumor types. The ever-evolving operational definition makes its classification sometimes difficult to define a cut point and ensure consensus across studies.
Who	Who does the selected impairment affect? Is it specific to a tumor type or common across different cancers/treatments?	It is common in a variety of tumor types, through different mechanisms.	While it may be attractive to select sarcopenia in all cancers, androgen deprivation therapy in prostate cancer versus surgery with chemoradiotherapy in head and neck cancer likely present different challenges to anabolism. Thus, recruiting both may introduce heterogeneity that will be difficult to control for.
When	Given the considerable financial, emotional, physiological burdens of undergoing anti-cancer therapy, discussions around the most appropriate time to intervene should have patient preferences and feasibility in mind in addition to physiological rationale.	Intervening as early as possible to reduce loss of muscle mass and function is important in delaying the resultant adverse health effects.	Intervening at diagnosis may be “easier” in prostate cancer with a relatively lower burden of treatment. In contrast, chemoradiation in head and neck is well known as quite toxic and all consuming, potentially impacting the likely success of an early intervention.

First, it is critical to be aware if one’s assessments are a direct measurement of the outcome in questions or comprise surrogate markers thought to reflect changes for said endpoint⁵². It is often impractical, or even impossible, to evaluate the true main outcome of interest in individual patients. For example, the time, resources, sample size and finances required to longitudinally assess the true risk of fractures (i.e. does a fracture happen or not) would be practically unfeasible. Thus, the use of known surrogates such as changes in bone mineral density, postural balance, etc. is necessary, but not without limitations, as several examples demonstrate that the relationship and pathway between a surrogate measure and the true endpoint may not be as direct, accurate or causal as implied⁵³.

Second, it is important to consider to which extent the choice of assessment methods, per se, has implications for the interpretation of the changes in the underlying physiological/psychosocial profile. For example, 1-repetition maximum (1-RM) tests in resistance training machines are almost universally used for measuring changes in muscle strength, but have a strong technical learning curve, where rapid improvements are observed primarily due to proficiency in technique and neuromuscular adaptation (i.e. co-activation and neural drive to relevant muscle groups), that are unlikely to transfer to other activities.

Third, the interpretation of change in an outcome using a given assessment method requires a reference to what would constitute a meaningful change. The concept of minimal clinically important difference (MCID) is often referred to as “the smallest difference that patients perceive as beneficial that would mandate in the absence of troublesome effects and excessive cost, a change in the patient’s management”^{54,55}. This concept is critical in exercise oncology to identify a magnitude

of change in outcomes that is considered meaningful to aid in the design and interpretation of trials. Additionally, these may also give us insight into program design in terms of trying to change outcomes of a certain magnitude. Specifically, they may give insight into the type, dose of exercise required, and the overall length of intervention. For example, changes in muscular strength may be achieved with resistance training of moderate loads in about 4 weeks, particularly in previously untrained individuals. However, meaningful changes in bone may require a higher load of resistance training and/or the inclusion of impact training and may not result in meaningful changes for at least 6 months. Multiple options for the estimation of MCID exist, including both statistical and expert opinion approaches⁵⁵. Ultimately, best practice would be to identify magnitude of change that would be interpreted as meaningful a priori. This would allow for a better structuring of the key training principles central to optimizing the outcome of interest, but also provide insight into the overall duration of the intervention. Finally, the interpretation of the magnitude of changes needs also to be attentive to the principle of regression to the mean, particularly important for outcomes known to fluctuate significantly, e.g. serum markers for glycemic control or subjective symptom scores. In some scenarios, where individuals are targeted specifically based on their “impaired” profile with e.g. high levels of fatigue, it is difficult to rule out spontaneous recovery, particularly once the burden of treatment has been lifted, which may have little to do with intervention. Whilst there is an ever-growing body of evidence reporting decline in a variety of physiological and psychosocial outcomes from various anti-cancer therapies, there is a paucity of research documenting and profiling the time course of recovery in these outcomes, once the burden of treatment has lifted.

Targeting the intervention to the endpoint

Individuals with cancer often present with unique physiological and psychosocial phenotypes and individual circumstances, which can require modifications to ‘standard practices’ when prescribing exercise training. Yet, considerations on overall design, delivery and monitoring of an exercise training program should still be based on universally applicable fundamental principles of exercise training and monitoring, which are often neglected in the oncology setting.

A common theme in the exercise oncology literature to date has been a poor attention to key principles of training with exercise trials⁵⁶⁻⁵⁹. Neil-Sztramko et al (2019) reported that principles of progression and overload were applied in 29% and 38% (respectively) of studies of exercise training in breast cancer⁵⁸. This was followed up with another report of principles of progression and overload being appropriately applied in 55% and 48% of studies of exercise training in prostate cancer⁵⁷. These statistics are quite alarming and allude to over half of exercise oncology trials failing to apply foundational principles of training. Incorporation of foundational principles of training (i.e. specificity, progression, overload, etc.) in exercise oncology trials is absolutely critical to maximize the response for outcomes of interest. It should also be noted that individuals with cancer often have a variety of physiological and psychosocial factors that fluctuate in nature, resulting in varying levels of preparedness or ‘readiness to train’, calling for a need to strategically modify training stress to match an individual’s propensity to train and response to that stress. Failing to adhere to these principles can have detrimental implications. For example, attempting to combat muscle wasting in sarcopenia by a walking intervention or concluding an intervention to be not-feasible simply due to poor timing and/or planning and/or programming can lead to wide discouragement and down-prioritizing of otherwise promising interventions.

In direct continuation of the need for better attention to training specific principles, another largely overlooked aspect in the exercise oncology literature is the concept of flexible programming and/or principles of rest and recovery. Individuals with cancer experience a variety of fluctuations in energy, sleep, and mood that are particularly pronounced during treatment. These, coupled with acute side effects of treatment such as nausea and appetite suppression, can impact both an individual’s preparedness for an exercise session and potentially their ability to respond and adapt to a given training stimulus. The variabilities in the presence and magnitude of these factors, particularly during treatment, emphasize the need to modify the exercise prescription in response to these fluctuations and provide an appropriate training stress. This process of modifying training in response to an individual’s objective or perceptual readiness to train is often termed “autoregulation”⁶⁰. There are a variety

of methods currently being examined as a way to autoregulate training. Current strategies include biochemical monitoring (most typically cortisol or testosterone), assessment of muscle damage, stress (heart rate variability) performance or perceptual/subjective questionnaires. This area of research is very much understudied, even less so in an oncological setting. There is continued debate and inconsistencies in relation to the optimal method of autoregulation, that balances accuracy, time, cost and resources. Nevertheless, the overarching concept of matching the intended training stress with an individual’s readiness and recovery holds merit within exercise oncology¹⁶. Most importantly, it may allow for appropriate rest and recovery between exercise sessions, that when paired with an appropriate training stress, could minimize injury risk and maximize outcomes. This is particularly important during active treatment periods, where the administration of anti-cancer therapy can result in declines in neutrophils, increasing the risk of infection.

An integrated component of a targeted exercise program is the framework, with which to follow how a planned intervention is executed, tolerated and possibly modified. From the more than 300 structured exercise trials published over the last three decades, an almost universal feature is the sole focus on “attendance” as a measure of compliance to the intervention. This practice may stem from the early overlap with behavioral research, where exercise participation (or physical activity time) per se, is the outcome of interest. However, when moving toward a targeted approach to a specific exercise dependent outcome, merely noting (and reporting) attendance is far from adequate to capture and evaluate overall physiological strain induced by intervention, when ultimately evaluating its efficacy (or lack thereof). The obvious need for improvement in this area has led to the development of novel metrics for reporting aerobic⁶¹ and resistance exercise⁶² dose and tolerability, using “exercise relative dose intensity (ExRDI)” in an attempt to capture the completed dose of exercise, relative to what was originally planned. Along with these metrics, there is also the need to discuss how and why the exercise dose was modified (illness, injury, fatigue, logistics, etc.). Examples of such frameworks were used by Scott et al (2018) in a feasibility trial of aerobic exercise in metastatic breast cancer. Using these metrics, they reported that the dose of exercise had to be modified or reduced in 49% of sessions, which would not have been captured using their attendance rate of 63% (where just attending the session would normally count as adherence). They were also able to use these metrics to highlight how aerobic exercise training at the dose and schedule tested in this study was not feasible for a large portion of individuals⁶³. This study highlights the advantages of using these concepts and metrics to report exercise dose in exercise oncology trials to 1) get a more accurate depiction of the tolerance to exercise in different patient populations,

2) understand the impact of exercise dose as it relates to why or why not an outcome changed, and 3) provide a more specific framework for exercise prescription⁶².

In summary, the operational framework for targeted exercise training in the oncology setting presented here includes interrelated considerations for the identification of relevant endpoints, appropriate evaluation assessments, and corresponding design, prescription and adaptation of the exercise intervention to optimize response. We believe this approach increases the chance for exercise effects to translate into ‘hard’ clinical benefits, i.e. improved treatment efficacy and/or tolerability, compared to the promotion of generic programs, which largely comprise current research activities and practice guidelines in the exercise oncology space.

Outcomes of interest and challenges in research design

A variety of clinically relevant outcomes in oncology have the potential to be modifiable through targeted exercise, such as low muscle mass, cardiovascular decline, and bone mineral density. Investigating targeted exercise interventions on specific outcomes is a complex and challenging line of inquiry. It's likely that advancement in this area will require a variety of approaches and studies designed to 1) understand biological mechanisms of action (i.e. pre-clinical testing); 2) testing the safety, feasibility and tolerability of different types/doses of exercise, 3) preliminary investigations into the impact of exercise on outcomes of interest that are used to inform whether further inquiry is warranted, and 4) large scale, randomized phase II trials adequately powered to detect changes in the outcome of interest⁶⁴.

Conclusion and perspectives

While the concept of targeted exercise prescription is well known, it is considerably underappreciated, understudied and underutilized in the oncology setting. With emerging evidence that pathophysiological features, known to be modifiable by exercise training, are critical intermediates for optimizing cancer treatment and outcomes, we believe exercise training has an untapped potential in clinical oncology beyond the behavioral aspects of reducing sedentary time and promoting general exercise guidelines.

However, the concept of utilizing a targeted exercise approach remains in its infancy. We are unaware of any studies published to date showing an exercise intervention: 1) was specifically designed a priori to improve a primary endpoint considered ‘treatment-limiting’ for the given cancer population,

2) successfully improved said endpoint and 3) subsequently led to improvements in (the a priori hypothesized) treatment outcome. With rapidly emerging advocacies promoting exercise as a standard option for all patients with cancer, we call for future research initiatives to consider relevant settings, where a targeted approach may be superior and/or more cost-effective, compared to generic exercise programs, and we propose the present framework can be utilized to advance such initiatives.

Competing interests

The authors declare no conflict of interests.

Author contributions

CMF and JFC contributed equally to the conceptualization, development and revision of the manuscript.

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